

## Addition of Formoterol or Montelukast to Low-Dose Budesonide: An Efficacy Comparison in Short- and Long-Term Asthma Control

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### Key Words

Asthma control · Budesonide · Formoterol · Montelukast

### Abstract

**Background:** Asthma is a chronic inflammatory disease of the airways. Inhaled corticosteroids are very important in anti-inflammatory treatment, but to a great extent they cannot control asthma alone. In addition to corticosteroids, long-acting  $\beta_2$  agonists and leukotriene antagonists are used for asthma control. **Objective:** In this study, the effect of the addition of formoterol and montelukast on asthma control in patients with moderately persistent asthma who were symptomatic while using a low dose of inhaled budesonide was compared. **Methods:** At the beginning of the study, 40 symptomatic patients with moderately persistent asthma used 400  $\mu\text{g}/\text{day}$  budesonide for a 4-week training period, and were then divided randomly into two groups, each composed of 20 persons. For the first group's treatment regime, inhaled formoterol (9  $\mu\text{g}$ ) twice a day was added, and for the second

group's treatment regime, one-dose oral montelukast (10  $\mu\text{g}$ ) was added. These patients were followed up for 8 weeks. The patients' peak expiratory flow (PEF) values measured in the morning and at night, changes in PEF, forced expiratory volume in 1 s, asthma symptom score and the symptom-relieving therapy used during the 12-week study period were recorded and evaluated in the clinic at the very beginning and at the end of each period.

**Results:** Before the study, the morning PEF value of the group for whom formoterol was added to budesonide (FB) was  $266.3 \pm 59.3$  liters/min, and in the group for whom montelukast was added to budesonide (MB), it was  $262.8 \pm 53.8$  liters/min ( $p > 0.05$ ). After the 8-week treatment period, the morning PEF values were found to be  $320.5 \pm 54.4$  liters/min in the FB group and  $293.3 \pm 52.4$  liters/min in the MB group; at the end of the study, it was seen that although there was an increase in morning PEF of  $54.2 \pm 15.2$  liters/min in the FB group, there was an increase of only  $30.5 \pm 25.3$  liters/min in the MB group ( $p < 0.0001$ ). Before the study, night PEF values were  $287 \pm 56.6$  liters/min in the FB group and  $283 \pm 48.5$  liters/min in the MB group ( $p > 0.05$ ). At the end of the treatment, the night PEF values were found to be  $331.5 \pm 56.1$  liters/min in the FB group and  $310 \pm 53.1$  liters/min in the MB group. At the end of the study, it was

We declare that we had no additional financial support or national funding for this study.

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observed that although there was an increase in night PEF of  $44.5 \pm 23.3$  liters/min in the FB group, there was an increase of only  $27 \pm 24.1$  liters/min in the MB group ( $p < 0.001$ ). Although asthma symptom scores and the use of symptom-relieving drugs showed similarities between the two groups at the beginning of the study, after treatment, the FB group had better results than the MB group with respect to these two parameters ( $p < 0.0001$  for both). It was also seen that the two treatments are tolerated equally well. **Conclusion:** FB treatment, which causes a considerable improvement in lung function, showed better asthma control than MB treatment in patients with moderately persistent asthma.

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## Introduction

The aims of asthma treatment are defined as prevention of all chronic and disturbing symptoms, provision of normal or near normal lung function, achieving normal daily life including exercise and physical activity, prevention of recurrent asthma attacks and minimizing the frequency of hospitalization or use of emergency services, by choosing drugs that have minimal or no adverse effects, meet the expectations of patients and their families with respect to treatment and satisfy the patients and their families [1, 2].

Inhaled corticosteroids (ICS) are the gold standard in anti-inflammatory treatment of asthma [1]. Although increasing the dose of ICS can be a treatment option, the local and systemic adverse effects of high-dose ICS make this alternative less valuable [3, 4]. Therefore, the addition of a second treatment with a supplementary effect mechanism enables better asthma control [1, 2, 5–8]. Recent studies have also supported the use of long-acting  $\beta_2$  agonists and ICS together [6–11]. An alternative approach is to add a leukotriene receptor antagonist to an ICS [12, 13]. Montelukast is a leukotriene receptor antagonist that improves asthmatic inflammation and prevents bronchoconstriction [14–16]. The addition of a long-acting  $\beta_2$  agonist or a leukotriene receptor antagonist to ICS has been shown to prevent exacerbations and improve the quality of life of asthma patients [17–19]. In some studies, the additive effects of ICS plus montelukast treatment have been found to be an alternative to increasing the dose of ICS in conditions in which ICS alone are inadequate [12, 20, 21].

The aim of this study was to investigate whether the addition of formoterol or montelukast to a low dose of

ICS was effective in the control of asthma in moderately persistent asthma cases, and to determine which drug should be preferred.

## Patients and Methods

### Patients

The study was carried out with 48 patients with moderately persistent asthma who presented to the Clinic for Chest Diseases of the Harran University Faculty of Medicine. 40 patients completed the study. The patients were diagnosed with asthma according to the diagnostic criteria of the international asthma consensus report [1, 2]. The patients who were included in the study had had persistent asthma symptoms for at least 1 year, had used ICS for at least 6 months, were 15–60 years of age and did not smoke.

### Study Design

During the training period, patients were included if their forced expiratory volume in 1 s ( $FEV_1$ ) or their peak expiratory flow (PEF) value was  $\geq 60\%$  or  $\leq 80\%$  of the expected value, if they had a  $\geq 15\%$  increase in  $FEV_1$  and mean morning PEF value  $\leq 85\%$  of maximum level after inhalation of a short-acting  $\beta_2$  agonist, if they used salbutamol more than twice a day or if their morning-night symptom score (these symptoms are described as symptoms if they are experienced at least twice a day or if they cause the patient to wake up at least twice a night) was  $\geq 2$  on 4 or less days in a week.

Pregnant or lactating women, patients with life-threatening asthma, patients hospitalized due to asthma within the previous 3 months and patients with accompanying upper or lower respiratory infections were not included in the study.

200  $\mu\text{g}$  of budesonide twice a day was given to all patients for 4 weeks (training period) at the beginning of the study. During the training period and the following 2 months (treatment period), oral or parenteral corticosteroid treatment, theophylline, anticholinergics, oral  $\beta_2$  agonists, all types of antihistamines, drugs which contain sodium cromoglycate or nedocromil sodium, and drugs that can make study complex were prohibited. Patients were allowed to use a short-acting  $\beta_2$  agonist (salbutamol 100  $\mu\text{g}/\text{puff}$ ) for symptomatic treatment, but only if they recorded the number of daily uses. 40 symptomatic patients with persistent asthma were divided randomly into two groups, each containing 20 patients. In the treatment of the first group, formoterol (9  $\mu\text{g}$ ) was given twice a day, and in the second group's treatment, one-dose oral montelukast (10  $\mu\text{g}$ ) was added; in this way, a formoterol-budesonide (FB; total daily dose 18–400  $\mu\text{g}$ ) treatment group and a montelukast-budesonide (MB; total daily dose 10–400  $\mu\text{g}$ ) treatment group were formed, and these two groups were followed up for 8 weeks.

Patients were evaluated in the clinic in the 1st, 4th, 8th and 12th weeks to ascertain their PEF values, change in PEF and  $FEV_1$  values, asthma symptom scores and use of symptom-relieving treatment during the study.

Patients recorded their own symptom scores, as well as their morning and night PEF values, the use of salbutamol for symptomatic relief of chest tightness, waking up at night, wheezing and dyspnea. The symptom scale was based on the Likert scale: 0 = asymptomatic; 1 = the presence of symptoms that do not disturb the patient; 2 = the presence of symptoms that disturb the patient, but not daily life; 3 = the presence of symptoms that not only disturb the patient but also

**Table 1.** Demographical and clinical features of patients

Features	FB group	MB group
Patients, n	20	20
Age, years	39.1 ± 12.4	33.2 ± 5.7
Sex (females/males), n	10/10	9/11
Duration of asthma, years	9 ± 8.8	8.1 ± 4
History of allergic rhinitis, n	12	14

prevent the daily activity of the patient for 1 day; 4 = the presence of symptoms that prevent daily activity for 2 or more days; 5 = the presence of symptoms that prevent the patient's daily activity during the whole week.

Asthma exacerbation was defined as the need for a drug that was not in the treatment protocol. Patients with asthma exacerbation were excluded from the study.

#### *Ethical Issues*

This work was performed according to the European regulations under the supervision of a bioethics consultant.

#### *Statistical Analysis*

All of the efficacy and safety analyses were carried out in a population of patients who were willing to undergo the treatment. All randomized patients, with the exception of those with missing diary data, were included in the analysis. The efficacy analyses were performed using an intention-to-treat approach, including all randomized patients with at least one baseline measurement and one after randomization. Results were summarized as absolute and percentage change from baseline with 95% confidence intervals. *p* values were rounded to three decimal places; *p* ≤ 0.05 was considered statistically significant.

The primary efficacy criterion was the morning PEF value, which was measured between 1 and 12 weeks. The comparison of the groups in terms of their morning PEF values between 1 and 12 weeks was performed using covariance analysis (ANCOVA), and sex, age, the beginning values and the effects of the treatment were taken into consideration.

The secondary efficacy criteria were the incidence and severity of exacerbations, the clinical FEV<sub>1</sub> values, the morning PEF values between 1 and 4, 5 and 8 and 9 and 12 weeks, all data recorded on the daily patient card in these weeks, the evening PEF values, the use of symptom-relieving salbutamol, and the diurnal change in the scores of symptoms that were experienced in the night- and daytime. The FEV<sub>1</sub> values and other secondary efficacy criteria that were recorded on the daily patient card were, as with the primary efficacy criteria, analyzed using ANCOVA.

The analysis of the morning PEF values between the 1st and 7th days was performed using ANCOVA in which sex and age, among other things, were taken into account.

Adverse events were monitored throughout the study. Investigators evaluated all clinical adverse events in terms of intensity, duration, seriousness, outcome and relation to test drugs.

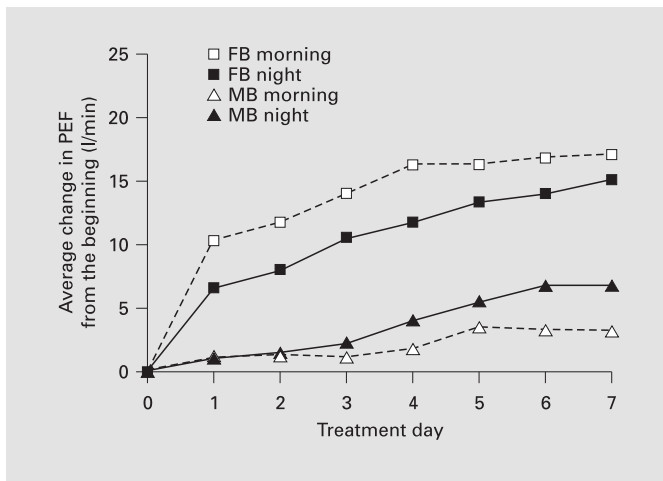
## **Results**

48 patients were initially included in the study. 6 of these patients were excluded from the study due to acute asthma exacerbation or use of other drugs; 2 patients were also excluded from the study because they did not come to the follow-up visits. Of the 40 patients who completed the study, 19 were female and 21 were male. Their mean age was 36.1 ± 9.98 years. There was no meaningful clinical difference between the two patient groups with respect to their baseline features. Demographical and clinical features of the patients are shown in table 1.

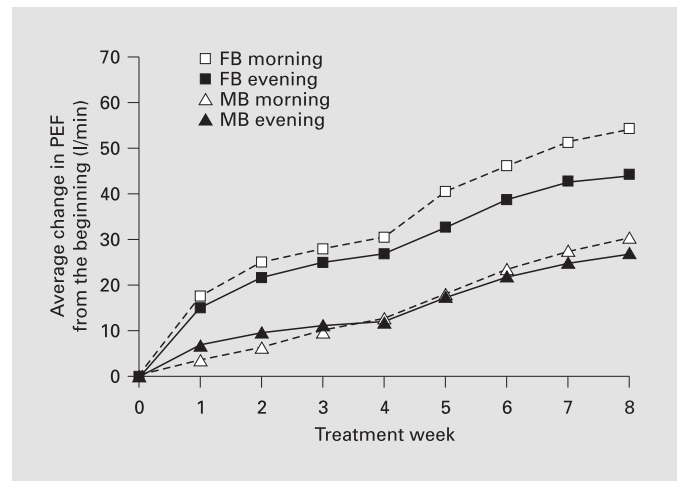
Morning PEF values showed statistical similarity between the two groups, who were randomized after the training period. Both groups showed improvements after the 8-week treatment period. Mean morning and night PEF values of patients treated with FB were found to be higher than the values of patients treated with MB during the 8-week treatment period (*p* < 0.0001 and *p* < 0.005, respectively).

Before the study, the morning PEF values were 266.3 ± 59.3 liters/min in the FB group and 262.8 ± 53.8 liters/min in the MB group (*p* > 0.05). After the 8-week treatment period, the morning PEF values were measured as 320.5 ± 54.4 liters/min in the FB group and 293.3 ± 52.4 liters/min in the MB group; at the end of the study, it was seen that there was an increase in morning PEF of 54.2 ± 15.2 liters/min in the FB group, but there was an increase of only 30.5 ± 25.3 liters/min in the MB group. There was a difference of 23.7 liters/min between the two groups, which was statistically significant (*p* < 0.0001). Before the study, the night PEF values were 287 ± 56.6 liters/min in the FB group and 283 ± 48.5 liters/min in the MB group (*p* > 0.05). After the treatment period, night PEF values were measured as 331.5 ± 56.1 liters/min in the FB group and 310 ± 53.1 liters/min in the MB group; at the end of the study, it was seen that there was an increase in night PEF of 44.5 ± 23.3 liters/min in the FB group, but there was an increase of only 27 ± 24.1 liters/min in the MB group. There was a difference of 17.5 liters/min between the two groups, which was statistically significant (table 2; *p* < 0.001).

Although improvement was seen in the morning and night PEF values of the two groups in the first week (*p* < 0.01 and *p* < 0.05, respectively), these improvements began earlier in the FB group, and a meaningful difference between the treatments was determined as early as the first day (*p* < 0.05 for both morning and night PEF values) (fig. 1). It was observed that there were more statistically significant improvements in the FB group than the MB



**Fig. 1.** Changes in the daily morning and night PEF values obtained with FB and MB treatments at the end of the first week.



**Fig. 2.** Average changes in the morning and night PEF values obtained with FB and MB treatments over the 8-week treatment period.

**Table 2.** Measurements of efficacy before and after treatment

	FB treatment	MB treatment	p value
Morning PEF values, l/min			
Beginning	266.3 ± 59.3	262.8 ± 53.8	>0.05
After treatment	320.5 ± 54.4	293.3 ± 52.4	<0.0001
Change after 8 weeks	54.3 ± 15.1	30.5 ± 25.3	<0.0001
Night PEF values, l/min			
Beginning	287 ± 56.6	283 ± 48.5	>0.05
After treatment	331.5 ± 56.1	310 ± 53.1	<0.0005
Change after 8 weeks	44.5 ± 23.3	27 ± 24.1	<0.0005
FEV <sub>1</sub> , liters/FEV <sub>1</sub> , %			
Beginning	2.4/71.2	2.38/69.7	>0.05
After treatment	2.76/81.9	2.57/75.3	<0.001
Change after 8 weeks	0.36/10.7	0.19/5.6	<0.001
β <sub>2</sub> agonist use, puffs/day			
Beginning	2.4 ± 1.5	2.4 ± 1.5	>0.05
After treatment	0.5 ± 0.8	1.9 ± 1.45	<0.0001
Change after 8 weeks	1.9 ± 0.5	0.5 ± 0.8	<0.0001
Morning symptom scores			
Beginning	3.1 ± 1.5	3.2 ± 1.6	>0.05
After treatment	0.5 ± 0.9	2.4 ± 1.2	<0.0001
Change after 8 weeks	2.6 ± 0.6	0.8 ± 0.7	<0.0001

group with regard to the morning and night PEF values ( $p < 0.001$  for both) between the 1st and 8th weeks and each of the 8 weeks as well (fig. 2).

Even though FEV<sub>1</sub>% values showed similarities after training treatment, improvement was seen in FEV<sub>1</sub>% and

FEV<sub>1</sub> values after 8 weeks of treatment in both groups. At the end of the treatment, changes in FEV<sub>1</sub> values of the FB group were found to be statistically significantly greater than those of the MB group.

The beginning mean value of FEV<sub>1</sub> in the FB group patients was 2.4 liters and the mean FEV<sub>1</sub> value after treatment was 2.76 liters; therefore, the treatment difference was 0.36 liters ( $p < 0.001$ ). At the beginning of the treatment period, the mean FEV<sub>1</sub>% value of patients treated with FB was 71.2%, and after 8 weeks, this value was 81.9%. Hence, the treatment difference was 10.7% ( $p < 0.001$ ).

The beginning mean value of FEV<sub>1</sub> in the MB group patients was 2.38 liters and the mean FEV<sub>1</sub> value after 8 weeks was 2.57 liters; therefore, the treatment difference was 0.19 liters ( $p > 0.05$ ). At the beginning of the treatment period, the mean FEV<sub>1</sub>% value of patients treated with MB was 69.7%, and after 8 weeks, this value was 75.3%. The treatment difference was 5.6% ( $p > 0.05$ ).

The percentage of asymptomatic days during 8 weeks was significantly higher in the FB group than in the MB group ( $p < 0.0001$ ). The improvement of symptom control in the FB group was faster than in the MB group in the first week of treatment ( $p < 0.0001$ ), and this difference was found to be meaningful even on the first day in terms of morning or night symptom scores ( $p < 0.0001$ ).

The number of days on which the patients did not use salbutamol was statistically lower in the FB group than in the MB group at all measurement times ( $p < 0.0001$ ).

In this study, the treatments were well tolerated in both groups. Some local adverse effects, which are potentially related to the drugs but did not affect the study, were seen. These adverse effects were oral candidiasis in 1 patient in each group, sore throat in 2 patients in the FB group and 1 patient in the MB group, voice problems in 2 patients in the FB group and 1 patient in the MB group, and headache in 1 patient in each group.

## Discussion

In this study, it was seen that the addition of formoterol to the treatment of patients with moderately persistent asthma whose asthma was not under control and who were using 400 µg/day budesonide showed better effects and significant improvement in the control of asthma when compared with the addition of montelukast. The effects of the two treatments were observed according to clinical end points determined previously. These end points were measurement of airway obstruction, symptom information recorded by the patients and exacerbation of asthma attacks [12].

Our study was performed in a single center in a homogeneous patient group. Due to this, the size of our patient

group and the duration of the study are low compared to other reports, and we acknowledge this. Although there are some studies whose duration was similar to ours [20, 22], there are also some whose duration was far longer than ours [23, 24] and others whose duration was shorter [25, 26].

Although there were no differences in PEF, FEV<sub>1</sub> values, asthma symptom scores and the use of a short-acting β<sub>2</sub> agonist, there was improvement in both groups after 8 weeks of treatment, and the results in the group treated with FB were statistically superior to the results of the MB group.

Mean morning and night PEF values increased to a significantly greater extent in the FB group than in the MB group. Accordingly, the total change from the beginning was  $54.2 \pm 15.2$  and  $44.5 \pm 23.3$  liters/min for the morning and night values, respectively, in the FB group, and  $30.5 \pm 25.3$  and  $27 \pm 24.1$  liters/min, respectively, in the MB group. These results showed that FB caused a greater improvement in lung function and had a better effect on control of asthma. Santanello et al. [27] stated that the minimal improvement threshold that could be realized by patients was 5% for PEF values and 10% for FEV<sub>1</sub> values. In accordance with this, we observed greater improvement in the FB group (for morning PEF 20.4%, for FEV<sub>1</sub> 10.7%), but the results of the MB group were also above the threshold levels (for morning PEF 11.6%, for FEV<sub>1</sub> 5.6%). However, there was a statistically significant difference between the FB and MB groups with regard to the PEF values and FEV<sub>1</sub> values.

The observed mean morning and night PEF values were confirmed at the end of the treatment period with the analysis results of FEV<sub>1</sub> values before treatment. These results were much better in the FB group than in the MB group, and the difference between the treatments was statistically significant ( $p < 0.001$ ).

There were no differences between the treatment groups at the beginning of the treatment period with regard to chest tightness, dyspnea, waking up at night, wheezing and other symptoms; at the end of the 8-week treatment period, although improvement was seen in the scores of both groups, there was a statistically significant improvement in the FB group. This shows that FB treatment controls asthma better than MB treatment and that FB treatment causes a greater decrease in symptom scores.

One of the important aspects of asthma control is the prevention of asthma exacerbation. Even though in our study asthma exacerbation was not experienced by patients of either group, it was seen that the use of the short-

acting  $\beta_2$  agonist was more frequent in the MB group. As a corollary to the patients' belief that salbutamol is effective against symptoms, the use of salbutamol was high in these patients. This fact leads to lower reporting of asthma symptoms in patients who use salbutamol more frequently. Hence, the use of symptom-relieving drugs can be a more objective criterion for the measurement of asthma symptoms [26, 28]. Some studies with a long duration have shown that the addition of a long-acting  $\beta_2$  agonist to ICS treatment significantly decreases the use of a short-acting  $\beta_2$  agonist [29]. These data show us that the additive effect of formoterol with ICS is greater than the additive effect of montelukast with ICS treatment [30]. The more frequent use of the short-acting  $\beta_2$  agonist in the MB group compared to the FB group shows us that these patients are more symptomatic and their asthma scores are higher; therefore, addition of formoterol to budesonide is more effective in the control of asthma symptoms.

Patients with persistent asthma who, at the same time, have continuing symptoms despite low-dose ICS, have been treated with drugs such as long-acting  $\beta_2$  agonists [6, 7, 26, 31, 32], theophylline [33, 34] and leukotriene antagonists [12], or have been treated by increasing the ICS dose. Increasing the ICS dose may cause many adverse effects [15, 32]. In addition, high doses of ICS alone may not be adequate for asthma control [15]. Therefore, international asthma guidelines suggest decreasing the ICS dose to a minimum. Hence, addition of another drug which has a supplementary mechanism is appropriate [1, 2].

In the present study, we showed that despite low-dose budesonide treatment, addition of formoterol to budesonide in symptomatic patients with moderately persistent asthma was superior to the addition of montelukast in the control of asthma and was associated with better treatment compliance. This long-lasting control highlights the potential steroid-retaining capacity of formoterol. These data are in concordance with national and international treatment guidelines that suggest the use of ICS at a dose as low as possible for asthma control [1, 2]. The clinical superiority of the FB treatment with low-dose ICS can be explained by the synergistic effect of these two drugs. By interacting with glucocorticoid receptors, formoterol enhances the activity of budesonide; on the other hand, the anti-inflammatory effect of budesonide complements the bronchodilatory effect of formoterol.

In the present study, we found that the improvement in lung function and symptom control with the FB treatment protocol was significantly high from the first day.

That the effect starts so quickly makes it easier for the patients to comply with the budesonide treatment [31, 35].

It is supposed that the regular use of a short-acting  $\beta_2$  agonist can worsen asthma control and masks the revival of inflammation; in this way, it may increase the rate of asthma exacerbation and severity. Therefore, there are some suspicions that maintenance therapy with a long-acting  $\beta_2$  agonist worsens asthma control [23]. In our study, we found that the use of low-dose budesonide was sufficient to control inflammation because there was no asthma exacerbation in either group. Similar results were obtained in studies that compared ICS plus long-acting  $\beta_2$  agonists with ICS alone [9, 26, 36, 37]. It was shown in the Formoterol and Corticosteroids Establishing Therapy study that the addition of formoterol to budesonide treatment decreases severe and mild exacerbation rates down to 63 and 62%, respectively [26]. As in other studies, Wilding et al. [34] showed that salmeterol (50  $\mu\text{g}$  twice a day) plus fluticasone propionate (250  $\mu\text{g}$  twice a day) is more effective for decreasing asthma exacerbation than fluticasone propionate (500–1,000  $\mu\text{g}$  twice a day) alone.

In some studies, it was shown that the addition of montelukast treatment in patients whose asthma could not be controlled helped to control asthma [12, 38]. In our study, the addition of formoterol to budesonide treatment caused a greater improvement in asthma control than the addition of montelukast to budesonide. This result is in accordance with previous studies [15]. Even though Nelson et al. [23] could not achieve the clinical improvement threshold by using montelukast and a low dose of ICS, they observed significant clinical improvement with a fluticasone propionate and salmeterol combination, and they also reported that the fluticasone propionate-salbutamol combination has a better effect on the control of asthma. Laviolette et al. [12] reported that the addition of montelukast treatment in symptomatic patients using inhaled beclomethasone had an additive effect on the control of asthma, and they recorded improvements of 10% for PEF and 0.15 liters for FEV<sub>1</sub> compared to baseline; however, these results did not reach the significant clinical improvement threshold. In our study, we reached the clinical improvement threshold in the MB group with improvements of 11.6% for PEF and 5.6% for FEV<sub>1</sub> values. In the FB group, however, there was 20.4% improvement in PEF and 10.7% improvement in FEV<sub>1</sub>, and these values were statistically significant when compared with those of the MB group ( $p < 0.0001$ ). These data show us that although the addition of montelukast to ICS treatment has a positive effect in asthma patients, it is weaker

when compared with the addition of formoterol, and our data also show that the use of formoterol and budesonide together significantly increased the symptom scores and pulmonary function of patients to a greater extent than the addition of montelukast to ICS treatment.

In conclusion, the addition of formoterol treatment in patients whose asthma can be controlled suboptimally by low-dose budesonide treatment has earlier effects and leads to greater control of asthma than the addition of montelukast. Therefore, formoterol should be preferred in symptomatic patients using budesonide.

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