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Comparing Budesonide and Fluticasone Propionate in Children with Moderate to Severe Asthma: A Pilot Randomized Controlled Trial

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ABSTRACT

The aim of asthma treatment is to reduce airway inflammation by avoiding environmental triggers and using daily anti-inflammatory medications. This study aimed to compare the effects of fluticasone propionate (FP) and budesonide (Bud) on the clinical symptoms and control of asthma in children with moderate to severe asthma.

In this open-label study, children with moderate to severe asthma were randomly selected to receive either FP 250 mcg or Bud 400 mcg for 3 months. Asthma control test scores were measured in both groups monthly. The clinical symptoms, drug adherence, and rescue medication were also evaluated.

A total of 50 patients with ages between 4 and 7 years old were included in the study (25 cases received Bud and 25 cases received FP). Asthma control test scores, daily and nocturnal symptoms, and cough rates were significantly improved in both groups. The average asthma control scores for the fluticasone group were 21.68±3.32 in the second month and 24.84±2.67 in the third month, whereas the budesonide group had scores of 18.52±3.32 and 22.48±4.12 during the same periods. These variances were statistically significant. Additionally, the requirement for salbutamol use was notably reduced in the fluticasone group compared to the budesonide group throughout all three months.

The efficacy of fluticasone propionate in decreasing the need for rescue medication and enhancing asthma control test scores was markedly superior to that of budesonide.

Keywords: Asthma; Budesonide; Children; Clinical trial; Fluticasone propionate

INTRODUCTION

Asthma is the most common chronic disease of childhood and is characterized by bronchoconstriction, edema, inflammation, and hyperresponsiveness of airways.[1] It is seen in 9.6% of children, most commonly in boys and African American and Hispanic children.[2,3] Clinical symptoms of asthma are the result of inflammation and variable airway obstruction and consist of recurrent wheezing, coughing, chest tightness,

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and dyspnea.[3,4] The prevalence of asthma in children is increasing,[5] causing more hospitalizations, emergency visits, and school absenteeism.[2,6] The heavy burden of medical costs of asthmatic patients suggests further emphasis on the management of the disease.[7] Asthma is best controlled by the combination of pharmacologic treatment, patient education, and reducing exposure to environmental allergens.[8] A combination of long-term controllers and short-term quick relief drugs are recommended for pharmacologic therapy.[4]

Inhaled corticosteroids are the most potent, safe, and well-tolerated drugs to control long-term symptoms of asthma.[4,9] They have fewer adverse effects compared to systemic glucocorticoids. Fluticasone Propionate (FP), Beclomethasone, ciclesonide, mometasone, and Budesonide (Bud) are commonly used Inhaled corticosteroids.[9] Each inhaled corticosteroid has specific characteristics.[10] lung depositions, bioavailability, clearance rate, protein binding fraction, volume of distribution, pharmacodynamics, and receptor binding affinity of various inhaled corticosteroids are different.[10,11] This makes the therapeutic and side effects of these drugs slightly different and therefore several studies have compared these inhalers.[12-16]

Fluticasone, a potent locally active glucocorticoid, relieves allergic inflammation by inhibiting interleukins, arachidonic acid, protein extravasation, and protease release.[17] The safety of fluticasone is well-known.[18] Compared to Budesonide it has less oral bioavailability and clearance but a greater half-life and volume of distribution.[9] Budesonide is a liposoluble drug that inhibits transforming growth factor-beta, prevents apoptosis, and has immunosuppressive properties. Budesonide decreases cellular infiltration and inhibits several cytokines and chemokines.[19]

A systematic review comparing budesonide, beclomethasone, and FP suggested that FP in half dose of BUD was more potent with significantly greater FEV1 and improvement of morning peak expiratory flow(PEF), but at the same dose has more side effects.[20] Some studies compared FP and BUD in adults but we found few studies comparing them in children.[18] To the best of our knowledge, we did not find a study comparing these two drugs in Iranian asthmatic children. This study is designed to compare the effect of fluticasone and Budesonide on clinical symptoms and asthma control in children with persistent asthma.

MATERIALS AND METHODS

We conducted a pilot randomized clinical trial on children with moderate to severe asthma for one year to evaluate the effectiveness of fluticasone in comparison with budesonide. The present randomized, parallel, clinical trial study,(allocation ratio 1:1), was performed at Moussavi Hospital, a tertiary- Medical University Center in Zanjan, from February 2019 to January 2020.

All children 4-7 years of age with a confirmed diagnosis of asthma, who have been hospitalized at least twice with asthma attack or had received beta-agonist medication without regular inhaled corticosteroids at least 2 months before hospitalization, defined as poorly controlled asthma were recruited. These patients were getting treatment for step 4 asthma according to NHA guidelines.[21]

Fifty children with moderate to severe asthma were enrolled after obtaining informed parental consent. Patients with heart disease, cystic fibrosis, chest anomalies, neurological and muscular problems, as well as children who were taking corticosteroid medicines were not included and patients who could not properly use the inhaler were excluded.

A questionnaire was initially designed to assess individual characteristics; Place of residence, Parental education, family history of atopy and smoking, symptoms, severity of illness, and duration of asthma.

Patients were divided by simple randomization into intervention and control groups by a nurse using a random-number table. The Fluticasone propionate (FP) inhaler group received 2 puffs of Flohale 125 micrograms (250 mcg) every 12 hours and the Budesonide (BUD) inhaler group received 2 puffs of Budecort 200 micrograms (400 mcg) every 12 hours by using a valved holding chamber (F.T.E co Pediatric Damyar With Pediatric Mask). This study was open-labeled and both inhalers were provided by one specific Pharmaceutical Company (Cipla, India).

The primary outcome was to determine the Asthma Control Test Score (ACT). For adherence evaluation, patients were followed up by phone or in person for 3 months. The parents also were asked to record the symptoms in the defined questionnaire (Standard Questionnaire: Asthma Control Test.[21-23] For 3 consecutive months, the Asthma Control Test Score, symptom recovery, the need for rescue medication, and reduction of drug doses in both groups were evaluated. Data were analyzed by SPSS software version 20.

Quantitative data were expressed by mean and standard deviation, percentage and frequency were used for qualitative data. The chi-square test was used to determine the relationship between qualitative variables and quantitative variables were analyzed by Friedmann tests. A significant level for all analyses was considered 0.05.

RESULTS

From 55patients, a total sample of 50 children aged between 4-7 years, hospitalized for an asthma attack at Moussavi Hospital in Zanjan, Iran from Februrary 2019 to January 2020, were selected and divided into two groups: 25 children receiving FP inhalers and 25 patients receiving Bud inhaler. Two patients from the fluticasone group and 3 patients from the budesonide group were excluded from the study because of irregular follow-up or changes in the type of drug during treatment (Figure 1).

The demographic characteristics in both groups were similar. There was no significant difference between the two groups regarding age, sex, duration of the disease, passive smoking, place of residence and parental education (Table 1).

There were no significant differences between the studied groups in terms of adherence in each three months (Table 2).

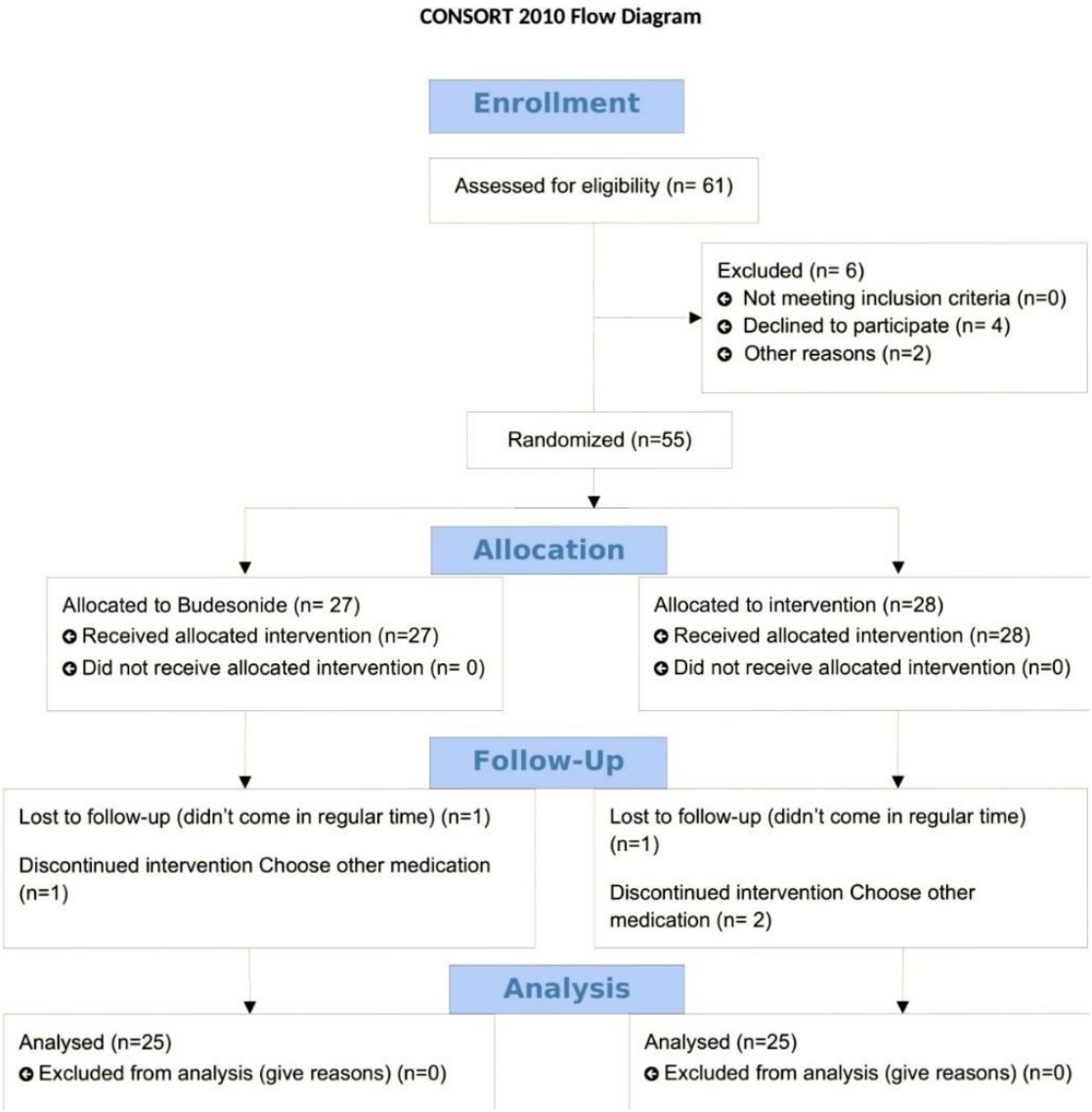

Figure1. The flow diagram of the clinical trial assessing the effectiveness of Budesonide vs Fluticasone in childhood asthma.

Table 1. Demographic data of patients in the budesonide and fluticasone receiving group

Variable	Budesonide group N (%)	Fluticasone group N (%)	*p*
Sex:			
Boy	13 (58%)	14 (56%)	0.777
Girl	12 (42%)	11 (44%)	
*Age (month):	55.68±16.31	53.96±17.87	0.724
Duration of disease(month)	7.36±6.23	9.56±9.15	0.325
Passive smoking:			
Yes	13(52%)	8(32%)	0.15
No	12(48%)	17(68)	
Place of residence:			
Urban	19 (76%)	15 (60%)	0.225
Rural	6 (24%)	10 (40%)	
Parental education:			
Undergraduate education	15 (60%)	13 (52%)	0.565
Bachelor's degree	9 (36%)	9 (36%)	
Masters or doctorate	1 (4%)	3 (12%)	
Maternal education:			
Undergraduate education	15 (60%)	16 (64%)	
Bachelor's degree	9 (36%)	7 (28%)	0.616
Masters or doctorate	1 (4%)	2 (8%)	

* Mean± standard deviation

Table 2. Comparing activity, cough, night problem, drug dose reduction, rescue medication, and adherence in patients receiving budesonide and fluticasone propionate during 3 months

Variable		Budesonide (N=25)	fluticasone propionate (N=25)	*p*
Daily Activity				
First month	No limitation	5 (20%)	10 (40%)	0.291
	Little limitation	13 (52%)	9 (36%)	
	Dissatisfied	7 (28%)	6 (24%)	
Second month	No limitation	6 (24%)	6 (24%)	0.572
	Little limitation	16(64%)	18 (72%)	
	Dissatisfied	3 (12%)	1 (4%)	
Third month	No limitation	17 (68%)	17 (68%)	0.572
	Little limitation	6 (24%)	7 (28%)	
	Dissatisfied	2 (8%)	1 (4%)	
Cough				
First month	No cough	1 (4%)	4 (16%)	0.404
	Sometime	18 (72%)	16 (64%)	
	Often	6(24%)	5 (20%)	
Second month	No cough	3 (12%)	5 (20%)	0.312
	Sometime	18 (72%)	19 (76%)	
	Often	4 (16%)	1 (4%)	
Third month	No cough	13 (52%)	15 (60%)	0.768
	Sometime	10 (40%)	9 (36%)	
	Often	2 (8%)	1 (4%)	

Night Problem				
First month	No	8(32%)	9(36%)	0.298
	Sometime	11(44%)	14(56%)	
	Often	6 (24%)	2(8%)	
Second month	No	10 (40%)	12(48%)	0.654
	Sometime	11 (44%)	11 (44%)	
	Often	4 (16%)	2(8%)	
Third month	No	18 (72%)	20 (80%)	0.777
	Sometime	6 (24%)	4 (16%)	
	Often	1 (4%)	1 (4%)	
Dosage change:				
First Month	Not decreased	15 (60%)	15 (60%)	1
	Decreased	10 (40%)	10 (40%)	
Second month	Not decreased	17 (68%)	13 (52%)	0.357
	Decreased	8 (32%)	12 (48%)	
Third month	Not decreased	9 (36%)	4 (16%)	0.229
	Decreased	16 (64%)	21 (84%)	
Rescue medication:	0	3 (12%)	7 (28%)	0.012
First month	1–3	3 (12%)	10(40%)	
	4–10	15 (60%)	4(16%)	
	>11	4 (16%)	4(16%)	
	0	1(4%)	9 (36%)	<0.001*
Second month	1–3	6(24%)	13 (52%)	
	4–10	16 (64%)	3(12%)	
	>11	2(8%)	0	
	0	3(12%)	14(56%)	0.001*
Third month	1–3	12(48%)	10(40%)	
	4–10	10(40%)	1(4%)	
	>11	0	0	
Adherence:				
First month		14(56%)	19(76%)	0.136
Second Month		20(80%)	21(84%)	0.713
Third Month		22(88%)	24(96%)	0.297

In the first month, the mean score of the asthma control test was 20.5±4.55 in the FP group compared to 18.08±4.36 in the BUD group. The results of the independent t-test showed that there was no significant difference between the mean scores of the asthma control test in the first month in the studied groups (p=0.059).

The mean scores of asthma control test in the second and third months in the fluticasone group were 21.68±3.32 and 24.84±2.67 compared to 18.52±3.32 and 22.48±4.12 in the budesonide group. However, The mean score of the asthma control test in the second and third month in the fluticasone inhaler group increased significantly compared to the budesonide inhaler group (p=0.001, p=0.020; respectively).

No significant difference in terms of the degree of difficulty in performing daily activities, reducing cough, and reducing nocturnal symptoms was observed between the two groups. However as shown in Table 2, the difficulty in performing daily activities and the amount of cough and nocturnal symptoms decreased significantly over 3 consecutive months in both groups (p<0.01).

According to Chi-square test, there was no significant difference between study groups in terms of drug dose changes during three months. However, the results of Freedman's test, showed that Bud dose did not

change significantly for 3 consecutive months (p=0.97) but FP dose decreased significantly over 3 consecutive months (p=0.028).

In both groups, the need for salbutamol (rescue medication) decreased significantly over 3 consecutive months (p<0.05), but as shown in Table 2, in the FP group, the need for salbutamol was significantly lower than in the budding group (p<0.05).

The changes between the 2 groups during 3 consecutive months were analyzed through repeated measurement tests. As shown in Table 3, we found a significant difference in ACT score (p<0.001) and salbutamol need (p=0.001).

During the study, no side effects were reported in the participants.

Table 3. Mean Asthma Control Test (ACT) score, in patients receiving budesonide and fluticasone during 3 month

ACT score	budesonide	fluticasone propionate	PV
First month	18.08±4.36	20.5±4.55	0.059
Second Month	18.52±3.32	21.68±3.32	0.001*
Third month	22.48±4.12	24.84±2.67	0.02*

DISCUSSION

This study was designed to compare the effect of FP and Bud on clinical symptoms and asthma control in children with persistent asthma. The results of our study showed that using both of these inhalers for three months, significantly improved asthma but there was a significant reduction of rescue medication use in the second and third month in patients receiving FP.

Karakoç et al, in Turkey, evaluated 96 children with moderate to severe asthma comparing the effect of half-dose fluticasone with beclomethasone and budesonide. It was found that although half-dose fluticasone could be effective in controlling the clinical symptoms of asthma, lung function parameters indicated that fluticasone was not twice as effective as budesonide and beclomethasone.[16] Due to the pharmacokinetics of the two inhalers and the fact that fluticasone has a longer half-life, (about 5 times compared to budesonide), this finding is somewhat justified and FP could be more effective. While higher esterification of BUD and increasing residence time in the target organ might induce longer and even better anti-inflammatory action of BUD.[9,10] A study by Kuo et al., to evaluate the effectiveness of Bud 400 mcg daily in comparison with FP 500 mcg in 5 to 18 years old patients with mild to moderate asthma was done. They found good asthma control in both groups with rapid improvement of lung function in the Bud group and a better reduction in exhaled nitric oxide in children receiving FP.[24] On the contrary, a study by Jenkins. In 2000 Australia compared two methods of treating asthma in 350 patients whose symptoms did not resolve despite treatment with lower doses of budesonide. In the first group, a fluticasone inhaler plus salmeterol 250 mcg was administered twice daily and the second group received a budesonide inhaler 800 mcg 2 times a day. The results of this study showed that combination therapy with salmeterol and fluticasone effectively improved daily and nocturnal symptoms and decreased the need for salbutamol in these patients.[25] The study of Lin on a multicentric single-blind randomized trial in China on 317 adult patients showed that 12-week treatment with FP and BUD increased the mean morning PEF but the difference between the 2 groups was not significant.[18]

In general, few studies have been performed on children to compare the effects of these two inhalers, and most studies have focused on adults, but the overall results are consistent with the results of the present study that demonstrates fluticasone inhaler as a newer treatment and better therapeutic effects than Bud and older drug such as beclomethasone propionate.[16,25-26]

Another finding in the present study was that the administration of a fluticasone inhaler was significantly reduced over 3 months, this result was not seen in the Bud group. Also, we compared the effect of these two inhalers on the number of daily symptoms in 3 consecutive months. The results showed that although both inhalers significantly reduced the difficulty in

performing daily activities, their effectiveness did not differ significantly.

In our study, both inhalers effectively reduced patients' coughs, but their effects did not differ significantly. The meta-analysis of Adams examined a total of 71 studies and concluded that despite the greater effect of fluticasone inhalers on beclomethasone and budesonide, the difference was not significant. All three inhalers improved morning and evening PEF and there was no difference in the rate of cough, pharyngitis, or hoarseness in patients.[20]

Finally, we looked at asthma control test scores in two groups and compared them. The results of our study showed that both inhalers significantly increased asthma control test scores, and the mean asthma control test score in the second and third months in the FP group increased significantly compared to the Bud group.

Although the effectiveness of FP in the reduction of drug dose, need for rescue medication and elevation of asthma control test was significant, some properties including higher half-life and volume distribution in comparison to Bud might increase our concern about the safety of prescribing higher doses of FP in younger children. On the other hand, adding long-acting beta-agonists and reducing the dose of FP in these children might mask the inflammatory process in infants and younger children and should be prescribed with caution.

A study was performed by Meltzer and colleagues to investigate the effectiveness and safety of Budesonide compared to placebo on 6- to 12-year-old children with asthma in Sweden in 2015. They showed that treatment with budesonide significantly improved morning PEF (peak expiratory flow) and expiratory volume, reduced the frequency of nocturnal awakening, and decreased the need for life-saving treatments or short-acting beta-agonists. Also; no serious side effects were reported with the use of budesonide.[27] Harrison and coworkers studied the systemic effects of FP and BUD given by dry powder inhalers in healthy and asthmatic subjects. They showed that FP has a greater effect on the hypothalamic-pituitary-adrenal axis especially in healthy subjects but this effect did not occur in the Bud group.[28] However, some research demonstrated that Fluticasone at an equivalent dose seems to inhibit growth less than beclomethasone and budesonide.[29] Considering the lower systemic bioavailability of FP than BUD, this result could be expected.[9]

The limitations of this study include the small sample size, the study was performed as a pilot study, and in addition, adherence was assumedly documented based on parent reports. Another limitation of this study was not determining the ACT score from the beginning and before the start of the study in the two groups.

In this study among young children with moderate to severe asthma, we found that the effect of FP in the reduction of rescue medication and increasing asthma control test scores was better than Bud's. However, both FP and Bud significantly reduced asthma symptoms and improved asthma control. Regarding few studies in children and limitations in the assessment of pulmonary function tests especially in young children, further studies with different doses and types of inhaled corticosteroids are recommended.

STATEMENT OF ETHICS

This project was approved by the Institutional Ethics Committee (IR, ZUMS, Rec, 1397. 315) and registered on IRCT (Iranian Registry of Clinical Trials); IRCTID: IRCT20100104002976N4.

FUNDING

Not applicable

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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