Original Article

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Inhaled Beclomethasone with or whiteout Montelukast in the Management of Pediatric Persistent Asthma

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ABSTRACT

BACKGROUND AND OBJECTIVE: Inhaled corticosteroid is the first line of treatment for asthma which has its own side effects. By contrast, Montelukast has fewer complications and is easier to use because of its tablet-like form. Hence, the present study aimed to compare the effectiveness of inhaled beclomethasone with and without oral Montelukast in the control of children's persistent asthma.

METHODS: This clinical trial study was performed on 84 children with asthma referring to Amirkola Children's Hospital in two groups. One group of patients received inhaled beclomethasone with Montelukast. The another group was treated with only inhaled beclomethasone alone. Before and 3 months after the treatment, FEV1, IgE, eosinophilia, night sleep quality, and school absenteeism status were measured in both groups.

FINDINGS: FEV1 values presented no significant difference between the two groups before the treatment, but it significantly increased in both groups three months after the treatment (p=0.000) (from 71.8±2.1 to 89.4±2.1 in the combinative treatment group and from 72±3 to 88.3±2.4 in the beclomethasone group). However, there was no significant difference between the two groups in this regard (p=0.146).

CONCLUSION: The results of this study showed that although the increase in FEV1 was similar in the two groups after treatment, but due to the better therapeutic acceptance in the combination therapy group, combination therapy could be used to control children's asthma.

KEY WORDS: *Beclomethasone; Montelukast; Asthma; Pediatrics*.

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Introduction

Asthma is the most common chronic respiratory disease that has been steadily rising over the past decade (1). The rate of hospitalization for children with asthma is also increasing. Poverty, environmental factors, psychological factors, and lack of access to health are extremely important in the development of asthma (2). Other risk factors are sex (the prevalence of asthma in boys is greater than that of girls), children born from asthmatic parents, a history of viral infections, low birth weight children, food allergy and allergen allergy (3). The most common form of asthma in children is intermittent asthma, defined as daily symptoms less than twice a week, and nocturnal symptoms less than twice a month that do not have activity limitation (4). Various approaches are available to treat asthma and control symptoms, including the use of beta-adrenergic agonists, inhaled corticosteroids, anti-leukotrienes and anti-IgE therapies (5).

The efficacy of using inhaled corticosteroids, such as high dose beclomethasone has been proven in stable and severe asthma (6). However, the use of inhaled corticosteroids is associated with several complications such as growth retardation (7, 8), sore throat, cough during inhalation, weakening or violence of voice and candidiasis in children (9). Leukotriene modulators such as montelukast and zofirluctate block the function of leukotriene. Bronchodilation occurs within a few hours after the first dose and is maximized within the first few days after consumption. The level of eosinophil in the circulation decreases in response to treatment with leukotriene receptor antagonists (5). However, when the indirect criteria for airway inflammation (such as eosinophilia in sputum and expiratory nitric oxide levels) are used to determine the outcome, the effect of leukotriene receptor antagonists on inflammation as compared to placebo has varied (12-10). Leukotriene receptor antagonists can be given once a day (in the case of montelukast) or twice a day (for zofirluctate) (13).

Short-term, double blind, placebo-controlled trials, improvement in pulmonary function, have shown better scores in the Asthma-related quality of life questionnaire and less asthma attacks among patients treated with leukotriene modulators (5). Overall, studies have shown contradictory effects of montelukast compared to placebo in the treatment of asthma, and given the complications associated with the use of inhaled corticosteroids, and on the other hand, given the use of montelukast in the form of a pill is more convenient than inhalable products in patients, the aim of this study was to compare the effect of inhaled beclomethasone with and without montelukast on the control of asthma in children.

Methods

This clinical trial study was conducted in 2016 and 2017 after approval by the Ethics Committee of Babol University of Medical Sciences with code MUBABOL.HRI.REC.1396.38 and registered at the clinical trial site with IRCT code: 1N2017092036286 in children with stable asthma referring to Amirkola Children's Hospital in two groups. Children aged 6-10 years with stable asthma symptoms who were referred during the study were included.

The onset of the sampling was from autumn, and in the event of a history of pulmonary infections, any underlying illness such as simultaneous cardiac disease, antihistamine consumption, not having any illness and taking other medications were excluded. The minimum number of samples, taking into account the percentage of admission 82% and 45% for the two groups of montelukast and beclomethasone according to the study of Maspero et al. (14) and with a=0.05 and B= 0.1 using the software (STATA) was 40 in each group, which was eventually studied in two courses of 42 people. Selection of patients with asthma based on inclusion and exclusion criteria was based on easy sampling, but the allocation of samples in two groups was Block Randomization with 4 blocks.

The criteria for asthma diagnosis were based on GINA criteria based on history-clinical examination and respiratory function tests. Patients with mild to moderate disease were included in the study. Patients in one group received 100ug of inhaled beclomethasone three times daily with Montelukast tablets 5mg daily and other group was treated with 100ug of inhaled

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beclomethasone three times daily. In this clinical trial study tests were performed by the relevant technician and interpreted by the relevant expert as blind. Before and 3 months after treatment, the FEV1, IgE, eosinophilia, night sleep quality, and school absenteeism status were measured in both groups. Improvement in FEV1 was considered as a primary outcome, and the quality of night sleep quality and school absenteeism was seen as a secondary outcome. The questionnaire was completed once before treatment and one month after treatment by a person. In the 3rd month study, the possible complications of Montelukast (headache, diarrhea, nausea, urticaria, etc.) were also recorded. The response to treatment was related to FEV1 more than 80% (15). Spirometry was performed by a spirometry device, and the age and gender of children were recorded. People with informed consent were enrolled. Data were analyzed by SPSS 20 software, Chi-square, t-test, paired t-test and McNemar tests. P <0.05 was considered significant. A histogram chart was used to check the normal distribution of quantitative variables such as age and FEV1 values.

Results

The mean age of patients in the combination therapy group (Montelukast with beclomethasone) was 7.9±1.3 years and in the treatment group, beclomethasone alone was 8.1±1.2 years (p=0.169). There was no significant difference in the distribution of children's gender and waking status from night-time sleep due to asthma in the two groups, but the absenteeism was significantly higher in beclomethasone group than in the Montelukast + beclomethasone group (Table 1). Accepting medical treatment in combination therapy group (100%) was significantly better than beclomethasone alone (71.4%) (p=0.000). There was no significant difference between FEV1 before treatment between two treatment groups, but FEV1 level was significantly increased in both treatment groups three months after treatment, but the increase in the two groups was similar and did not show significant difference (Table 2).

There was no significant difference in the distribution of IgE status before treatment between the two treatment groups, but the percentage of normal IgE status in the combination therapy group was significantly higher than that of beclomethasone alone. Also, IgE level after treatment was significantly improved in both treatment groups compared to pre-treatment, and percentage of cases with normal IgE increased, and there was no significant difference in the distribution of eosinophilia before treatment between the two treatment groups. However, the percentage of cases of normal eosinophilia in the combination therapy group was significantly higher than that of beclomethasone alone. Also, eosinophilia was significantly improved in both treatment groups compared to pre-treatment, and the percentage of cases with normal eosinophilia was increased. Even in one case, in the beclomethasone group alone, elevated eosinophilia was lower at baseline than the normal (Table 3).

Table 1. Comparison of the status of patients when entering the study in terms of sex, waking up from sleep and absence from school due to asthma in two treatment groups

Variable		Montelukast+beclomethasone N(%)	Beclomethasone N (%)	p-value
Sex	Boy	19(45.2)	24(57.1)	0.383
	Girl	23(54.8)	18(42.9)	
Waking up from night sleep	Yes	14(33.3)	19(45.2)	0.372
	No	28(66.7)	23(54.8)	
Absence from school due to asthma treatment	Yes	5(11.9)	16(38.1)	0.011
	No	37(88.1)	26(61.9)	

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Table 2. Distribution of FEV1 status before and after treatment in two treatment groups in children with asthma

FEV 1	Montelukast + beclomethasone Mean±SD	Beclomethasone Mean±SD	pvalue
Befor treatment	71.8±2.1	72±3	0.679
Three month after treatment	89.4±2.1	88.3±4.4	0.156
p-value	0.000	0.000	
The difference befor and after	17.6±2.8	16.2±5.1	0.146

Table 3. Distribution of IgE status and eosinophilia before and after treatment in two treatment groups in children with asthma.

IgE	Montelukast + beclomethasone N (%)	Beclomethasone N(%)	p-value
IgE before treatment			
normal	14(33.3)	11(26.2)	0.634
increased	28(66.7)	31(73.8)	
IgE Three month after treatment			
normal	41(97.6)	19(45.2)	0.000
increased	1(2.4)	23(54.8)	
p-value	0.000	0.008	
Eosinophilia before treatment			
normal	12(28.6)	10(23.8)	0.804
increased	30(71.4)	32(76.20)	
Eosinophilia three months after treatment			
normal	34(81)	17(40.5)	0.000
increased	8(19)	25(59.5)	
p-value	0.000	0.016	

Discussion

The results of this study showed that there was no significant difference between FEV1 levels before treatment between the two treatment groups, but FEV1 level was significantly increased in both treatment groups three months after treatment, but the increase in the two groups was similar and there was no significant difference. However, accepting medical treatment in the combination therapy group was significantly better than beclomethasone alone. In a study by Stelmach et al on 76 children aged 6 to 14 years old with asthma, the effect of adding montelukast on the rate of inhaled corticosteroid use was evaluated in a double-blind clinical trial study. A treatment group received inhaled corticosteroid with montelukast and the other group was treated with inhaled corticosteroid plus placebo. The results of the study showed that the addition of montelukast to routine inhalation therapy significantly reduced the frequency of asthma attacks but had no significant effect on pulmonary function (16) which is similar to results of our study. In a systematic review conducted by Massingham et al. with the aim of comparing the effect of montelukast with inhaled corticosteroids on asthma control, of 214 articles, 8 articles had systematic review criteria, of which 4 articles mentioned the better effect of corticosteroid versus compared to montelukast, while in 4 studies there was no significant difference between the effect of montelukast and inhaled corticosteroids (17). In study of Kloepfer et al., there was no significant difference in

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the reduction of lower respiratory symptoms between the two groups receiving montelukast and placebo (18). Concomitant with the results of this study and others, similar effects have been observed with other inhaled corticosteroids.

In a clinical trial conducted by Olszowiec-Chlebna et al. with the aim of investigating the effects of inhaled corticosteroid in two different doses and montelukast on clinical signs and lung function in children with newly diagnosed asthma. Sixty-five children with newly diagnosed asthma were randomly assigned into three groups as double blind. After 6 months of treatment with different doses of inhaled budesonide and montelukast, asthma control and lung function were significantly improved in three treatment groups. But there was no significant difference between the groups (19).

In general, the results of this study and other available reports suggest no significant difference in the combination therapy compared with inhaled corticosteroid monotherapy on the parameters of lung function tests in patients with asthma, however adding an anti-leukotriene drug improves the quality of life and changes waking up from sleep at night. In a study by Robertson et al on 220 children aged 2-14 years with intermittent asthma, nocturnal wake-ups in the group that took montelukast for 7 days were lower than the placebo group by 8.6% (20). Since it plays an important role in allergic immune responses, the reduction of free IgE levels is a significant target in the treatment of allergic diseases (21).

The results of this study showed that there was no significant difference in the distribution of IgE status before treatment between the two treatment groups. However, the percentage of normal IgE status in the combination therapy group was significantly higher than beclomethasone alone. Also, IgE level after treatment was significantly improved in both treatment groups compared to pre-treatment, and percentage of cases with normal IgE was increased. In a random double blind clinical trial conducted by Stelmach et al. 51 children with newly diagnosed asthma were randomly assigned to receive inhaled budesonide (in two different doses of 400 or 800 micrograms) or montelukast for 6 months. The initial outcome was the total and specific serum IgE level before and after treatment. After 6 months of treatment, high dose budesonide and montelukast resulted in a decrease in total IgE and specific IgE and a moderate dose of inhaled corticosteroid did not affect the total and specific IgE levels (21), which is similar to the results of this study.

The results of this study showed that distribution of eosinophilia status before treatment was not significantly different between the two treatment groups. However, the percentage of cases with normal eosinophilia in the combination therapy group was significantly higher than that of beclomethasone alone. Also, eosinophilia was significantly improved in both treatment groups compared to pre-treatment, and the percentage of cases with normal eosinophilia was increased. In a study by Takemura et al. in Japan, the effects of 10 mg montelukast daily for 4 weeks were evaluated on 23 patients with cough variant asthma, and it was observed that montelukast significantly decreases the cough, sputum eosinophil count, and hypersensitivity to cough (22).

One of the limitations of the present study was the missing of eosinophilic sputum measurement, in which blood eosinophilia was studied instead. Also, other limitations of this study is the duration of the study. Therefore, studies with more sample size and longer follow-up are recommended. The results of this study showed that although the increase in FEV1 was similar in the two groups after treatment, but due to the better therapeutic acceptance in the combination therapy group, combination therapy could be used to control persistent asthma in children.

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References

1.Mohammadzadeh I, Ghafari J, Barari Savadkohi R, Tamaddoni A, Esmaeili Douki MR, Alizadeh Navaei R. The prevalence of asthma, allergic rhinitis and eczema in north of Iran. Iran J Pediatr. 2008; 18(2): 117-22.

2.Mohammadzadeh I, Mohammadi M, Khodabakhsh E. The effect of nebulised salbutamol plus magnesium sulfate in comparison with nebulised salbutamol plus normal saline in acute asthmatic attack in children. J Babol Univ Med Sci. 2014; 16(3):7-12. [In Persian]

3.Moussa MA. Factors accociated with asthma in school children. Eur J Epidemiol. 1996; 12(6):583-8.

4.Kliegman R. Stanton B, Geme J, Schor N, Behrman R. Nelson text book of pediatrics. 19th ed. Philadelphia: Saunders Elsevier. 2011; p. 780- 1, 784.

5.Fanta CH. Asthma. N Engl J Med. 2009;360(10):1002-14.

6.Adams N, Bestall J, Jones PW. Budesonide at different doses for chronic asthma. Cochrane Database Syst Rev. 2001;4: CD003271.

7.Szefler S, Weiss S, Tonascia J, Adkinson NF, Bender B, Cherniack R, et al. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med. 2000; 343:1054-63.

8.Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Pediatrics 2000;106(1):e8.

9.DelGaudio JM. Steroid inhaler laryngitis: dysphonia caused by inhaled fluticasone therapy. Arch Otolaryngol Head Neck Surg. 2002;128(6):677-81.

10.Pizzichini E, Leff JA, Reiss TF, Hendeles L, Boulet LP, Wei LX, et al. Montelukast reduces airway eosinophilic inflammation in asthma: a randomized,controlled trial. Eur Respir J. 1999;14(1):12-8.

11.Minoguchi K, Kohno Y, Minoguchi H, Kihara N, Sano Y, Yasuhara H, et al. Reduction of eosinophilic inflammation in the airways of patients with asthma using montelukast. Chest 2002;121:732-8.

12.Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC,et al. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 2005;352(15):1519-28.

13.Pajaron-Fernandez M, Garcia-Rubia S, Sanchez-Solis M, Garcia-Marcos L. Montelukast administered in the morning or evening to prevent exercise-induced bronchoconstriction in children. Pediatr Pulmonol. 2006;41(3):222-7.

14.Maspero JF, Dueñas-Meza E, Volovitz B, Pinacho Daza C, Kosa L, Vrijens F, et al. Oral montelukast versus inhaled beclomethasone in 6- to 11-year-old children with asthma: results of an open-label extension study evaluating long-term safety, satisfaction, and adherence with therapy. Curr Med Res Opin.2001;17(2):96-104.

15.Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J. 2015; 46(3):622-39.

16.Stelmach I, Ożarek-Hanc A, Zaczeniuk M, Stelmach W, Smejda K, Majak Pet al. Do children with stable asthma benefit from addition of montelukast to inhaled corticosteroids: randomized, placebo controlled trial. Pulm Pharmacol Ther. 2015; 31:42-8.

17.Massingham K, Fox S, Smaldone A. Asthma therapy in pediatric patients: a systematic review of treatment with montelukast versus inhaled corticosteroids. J Pediatr Health Care. 2014; 28(1):51-62.

18.Kloepfer KM, DeMore JP, Vrtis RF, Swenson CA, Gaworski KL, Bork JA, et al. Effects of montelukast on patients with asthma after experimental inoculation with human rhinovirus 16. Ann Allergy Asthma Immunol. 2011; 106(3):252-7.

19.Olszowiec-Chlebna M, Majak P, Brzozowska A, Bobrowska-Korzeniowska M, Jerzynska J, Stelmach I. Effect of inhaled steroid and montelukast on clinical symptoms in children with newly diagnosed asthma: a pilot study. Pediatr Allergy Immunol. 2010; 21(4 Pt 2):e687-90.

20.Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. Am J Respir Crit Care Med. 2007; 175(4):323-9.

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[DOI: 10.18869/acadpub.jbums.20.7.7]

21.Stelmach I, Bobrowska-Korzeniowska M, Majak P, Stelmach W, Kuna P. The effect of montelukast and different doses of budesonide on IgE serum levels and clinical parameters in children with newly diagnosed asthma. Pulm Pharmacol Ther.2005;18(5):374-80.

22.Takemura M, Niimi A, Matsumoto H, Ueda T, Matsuoka H, Yamaguchi M, et al. Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. Respiration 2012;83(4):308-15.

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