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Original Article

# Anti-leukotriene compared to inhaled corticosteroid for recurrent wheezing in children under five years of age: A randomized clinical trial

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**Abstract**

**Introduction:** Asthma is the common chronic disease in childhood. One of the major symptoms of asthma in children is wheezing. According to the international guidelines, inhaled corticosteroid (ICS) is prescribed for treating recurrent wheezing in children less than five years. However, due to poor adherence, high cost, and possible side effects of ICS in young children, anti-leukotrienes are recommended as a safe initial treatment for recurrent wheezing. Therefore, we performed this study to compare anti-leukotriene versus ICS in treating recurrent wheezing in children less than five years.

**Methods:** We enrolled 68 patients less than five years old with recurrent wheezing (more than three times over the past year) and mild persistent asthma in this randomized controlled clinical trial. The patients were randomly divided in a 1:1 ratio into two groups. Group 1 was treated by ICS 50 mcg twice daily and group 2 was received montelukast 4 mg granules daily. The patients followed up for six months and the results of the two groups were compared.

**Results:** Thirty-four of 68 patients received montelukast and 34 patients received ICS. In montelukast and ICS group, 23 (68%) and 20 (59%) patients were boys, respectively. The frequency of wheezing decreased significantly in patients receiving montelukast ($P<0.001$) as well as ICS ($P<0.001$). However, there were no differences between two groups in the efficacy of treatment ($P=0.38$).

**Conclusion:** In children less than five years with mild persistent asthma, both montelukast and ICS were effective with no differences between groups in the efficacy of treatment.

## Introduction

Asthma is a common chronic disease in childhood, affecting 10%-15% of children. Approximately 40% of preschool-age children have wheezing, but only 10% of them may have persistent asthma.[1] Diagnosis of asthma in under five years is based on symptoms such as recurrent wheezing, cough, dyspnea, and airway hyperresponsiveness with the positive response to bronchodilators.[2] Asthma diagnosis with pulmonary function test (PFT) or evaluation of airway inflammation is not common in preschool children.[3,4]

Inhaled corticosteroids (ICSs) are the most effective anti-inflammatory drugs for controller therapy of persistent pediatric asthma which decrease mortality and morbidity of asthma, improve lung function, and reduce exacerbation of airway hyper-responsiveness.[5] Side effects due to local deposition of ICS in the oropharynx and larynx are topical dysphonia and candidiasis. In addition, long-term side effects of high dose ICS are hyperglycemia, impaired growth, decreased bone mineral density, hypothalamic-pituitary-adrenal axis suppression.[6]

Leukotriene is an important inflammatory mediator in asthma. Recently, anti-leukotrienes such as montelukast, zafirlukast, zileuton, etc., are being studied as an anti-inflammatory drug in the treatment of asthma. Montelukast is a specific leukotriene receptor antagonist (LTRA), and it is the only LTRA approved for young children.[7] Montelukast is administered orally in a single daily dose and has no negative effect on growth, bones, or the adrenal system. Side effects of montelukast in the usual dose in children are rare, but headache, nausea, abdominal pain, and pharyngitis may occur.[8,9]

Most international guidelines for asthma and recurrent wheezing recommend treatment with low dose ICS as the preferred drug for children under five years, and LTRA is an alternative drug.[10] Due to the several side effects

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and complications of ICS use in children, we aimed to compare the therapeutic product of anti-leukotriene and ICS for controller treatment in recurrent wheezing and mild persistent in children under five years old.

## Methods

### *Trial design and setting*

In this randomized controlled trial, we enrolled patients referred to Tabriz children's hospital clinics during one year. After approving the study protocol by the ethics committee of Tabriz University of Medical Science, 68 children under five years old with recurrent wheezing (more than three times over the past year) or mild persistent asthma based on NIH guideline (daily symptoms occur several times per week but not daily and 2 or less nocturnal symptoms per month) were included in the study. The patients were randomly divided into two equal groups with Rand List and parallel allocation (1:1). Inclusion criteria were patients under five years who had recurrent wheezing more than three times over the past year with or without fever and mild persistent asthma.

Furthermore, we excluded patients with cystic fibrosis and a history of congenital heart disease and who had anatomical anomalies such as tracheobronchomalacia, vascular ring, and gastroesophageal reflux.

The present study was performed according to the Institutional Committee for the Protection of Human Subjects, which was adopted by the 18th World Medical Declaration of Helsinki, Finland and its later amendments (Declaration of Helsinki). Written informed consents were obtained from all parents of subjects.

### *Intervention*

Group 1 was treated with inhaled fluticasone 50 mcg twice daily with a spacer device with a face mask, and group 2 was treated by daily 4 mg montelukast granules in the evening.

### *Outcome evaluation*

Patients followed up for six months, and the results of the two groups were compared together. A decrease in the number of wheezes was considered as the response to the treatments.

### *Statistical analysis*

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 18. The quantitative variables were presented with descriptive statistics by mean ± standard deviation (SD), while frequency and percentage (%) were used for qualitative variables. Chi-Square test was used to compare qualitative data, and quantitative data were compared by independent samples t-test. A $P$ value < 0.05 was considered to be statistically significant.

## Results

A total of 68 patients who enrolled in this study, 63.23% were boys, and 36.76% were girls. There was no statistically significant difference in gender ($P = 0.61$). Twenty (59%) patients in group 1 (fluticasone group) were male, and 14 (41%) were females. In group 2 (montelukast group), 23 (68%) were males, and 11 (32%) were females.

Twenty-five patients (36.7%) had wheezing symptoms at sleep, 64 (94.1%) when resting, and 37 patients (54.4%) when crying. In addition, 50% of patients had a history of passive smoking, 41% had a familial history of asthma, and 73% had a familial history of atopy. There was no statistically significant relationship between wheeze in children under five years and familial history of asthma, atopy, and passive smoking ($P > 0.05$) (Table 1).

After six months of treatment with inhaled fluticasone 82.4% of patients had significant improvement ($P < 0.001$). Moreover, in montelukast group 73.5% of patients were showed a significant response to treatment ($P < 0.001$) after six months of intervention (Table 2).

There was no statistically significant difference between the response to the treatments in the two groups of patients receiving either inhaled fluticasone or montelukast ($P = 0.38$).

## Discussion

The present study evaluated the efficacy of two treatment options including ICS and montelukast, as per Global Initiative for Asthma (GINA) treatment guidelines, to manage asthma in children. Our results indicated significant improvement of wheezing in less than five years old children with ICS as well as montelukast with no differences in the efficacy of treatment between groups.

Wheeze is the most common symptom in childhood that may be accompanied by cough and dyspnea. Also, wheeze is a common cause of hospitalization and frequent references to the pediatric emergency department.[11] Treatment of early life asthma is important to prevent irreversible lung damage, decreased lung function, and resistant asthma.[12]

ICSs play major role in treating asthma, specifically in

**Table 1.** Effect of familial history and smoking on wheezing in children under five years

| Variable | Yes No. (%) | No No. (%) | *P* value* |
|---|---|---|---|
| Being a passive smoker | 34 (50%) | 34 (50%) | 1 |
| Having a familial history of Asthma | 28 (41.17%) | 40 (58.83%) | 0.148 |
| Having a familial history of atopy | 50 (73.5%) | 18 (26.5%) | 1 |

* Chi-square test.

**Table 2.** Effect of treatment with fluticasone and montelukast

| Response to treatment | Fluticasone group (n = 34) | Montelukast group (n = 34) |
|---|---|---|
| Yes | 28 (82.4%) | 25 (73.5%) |
| No | 6 (17.6%) | 9 (26.6%) |
| *P* value* | < 0.001 | < 0.001 |

* Chi-square test

older children, reducing airway inflammation.[13] Based on GINA guidelines, ICSs are first-line treatment for asthma, and anti-leukotrienes are alternative or additional therapy in mild persistent asthma. Daily symptoms that occur several times per week but not every day and infrequent night symptoms are classified into mild persistent asthma.[14] We suggest therapeutic effects of montelukast and low dose fluticasone in mild persistent asthma in children under five years are comparable. This study demonstrates that oral montelukast and inhaled fluticasone are similarly effective in treating mild persistent asthma in children under five years and the effect of both drugs was not statistically different ($P=0.38$). In a recent study, patients with mild persistent asthma who had received montelukast had a better response, better adherence, and fewer exacerbations than budesonide inhaler recipients.[15]

First-line use of anti-leukotrienes has beneficial effects on therapy and control of mild asthma through broncho-protection and reducing airway inflammation.[16] Also, anti-leukotrienes are an additional therapy to ICS for poorly controlled cases. [17]

Different types of respiratory virus infections can be the initiator of wheeze. All of our patients had cold symptoms at the first visit. Similar to other studies, our results show that montelukast decrease viral-induced exacerbations in young children.[18]Based on a previous study, wheezing and the shortness of breathing symptoms due to exercise were reduced in patients treated by montelukast.[19]Also, our findings confirm that montelukast is a safe and effective drug for exercise-induced asthma. Several studies reported that the daily use of 4 mg montelukast effectively reduced daily and nightly symptoms and decreased the need to inhale short-acting beta 2-agonist (SABA) and oral corticosteroid for relief of symptoms in children 2-5 years, the same as the result of our study.[14]

This study was performed to find a safe, low-cost, available, and low side effect treatment regimen. According to the results of this study, we can choose montelukast as an effective drug for the treatment of wheezing or mild asthma in children instead of using ICSs. The limitations of this study were the small sample size and short follow-up period that was only six months.

## Conclusion

According to the results of the present study, the therapeutic effect of fluticasone and montelukast had no significant statistical difference on wheezing reduction in children less than five years. However, regarding numerous side effects of ICS and the lack of significant difference in the therapeutic effects of two drugs, we recommend using montelukast because of its safety and effectiveness and oral administration. Moreover, it is suitable for children who cannot use ICSs properly.

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### Study Highlights

***What is current knowledge?***

- Treatment with low dose inhaled corticosteroid (ICS) is the preferred drug for children under five years in asthma and recurrent wheezing, and leukotriene receptor antagonist (LTRA) is an alternative drug. However, ICS had several side effects and complications.

***What is new here?***

- There was not significant statistical difference between fluticasone and montelukast in wheezing reduction in children less than five years. Therefore, montelukast because of its safety, effectiveness, and oral administration could be a preferable treatment in under five years' children.

**Authors' Contribution**

**Conceptualization:** Mahnaz Sadeghi-Shabestari, Azar Dastranji.
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**Competing Interests**

The authors declare that we have no conflicts of interests.

**Ethical Approval**

The ethics committee of Tabriz University of Medical Sciences, Iran (IR.TBZMED.REC.90/1-4/16) approved this study, and it is registered at the Iranian Registry of the clinical trials (identifier: IRCT201204099429N1).

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**References**

1. Kovesi T, Schuh S, Spier S, Bérubé D, Carr S, Watson W, et al. Achieving control of asthma in preschoolers. CMAJ. 2010;182(4):E172-83. doi: 10.1503/cmaj.071638.
2. van Aalderen WM, Sprikkelman AB. Inhaled corticosteroids in childhood asthma: the story continues. Eur J Pediatr. 2011;170(6):709-18. doi: 10.1007/s00431-010-1319-z.
3. Pedersen SE, Hurd SS, Lemanske RF Jr, Becker A, Zar HJ, Sly PD, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. Pediatr Pulmonol. 2011;46(1):1-17. doi: 10.1002/ppul.21321.
4. Bhatt JM, Smyth AR. The management of pre-school wheeze. Paediatr Respir Rev. 2011;12(1):70-7. doi: 10.1016/j.

prrv.2010.09.001.
5. Castro-Rodriguez JA, Rodriguez-Martinez CE, Ducharme FM. Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: a systematic review. Pediatr Pulmonol. 2018;53(12):1670-7. doi: 10.1002/ppul.24176.
6. Pelewicz K, Miśkiewicz P. Glucocorticoid withdrawal-an overview on when and how to diagnose adrenal insufficiency in clinical practice. Diagnostics (Basel). 2021;11(4):728. doi: 10.3390/diagnostics11040728.
7. Lee YJ, Kim CK. Montelukast use over the past 20 years: monitoring of its effects and safety issues. Clin Exp Pediatr. 2020;63(10):376-81. doi: 10.3345/cep.2019.00325.
8. Paggiaro P, Bacci E. Montelukast in asthma: a review of its efficacy and place in therapy. Ther Adv Chronic Dis. 2011;2(1):47-58. doi: 10.1177/2040622310383343.
9. Harmanci K. Montelukast: its role in the treatment of childhood asthma. Ther Clin Risk Manag. 2007;3(5):885-92.
10. Helen K, Leonardo B, Eric D, Louis P. Christopher B, Guy B. Global Strategy for Asthma Management and Prevention. Global Initiative for Asthma (GINA); 2021. p. 159.
11. Chavasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Persistent wheezing in infants with an atopic tendency responds to inhaled fluticasone. Arch Dis Child. 2001;85(2):143-8. doi: 10.1136/adc.85.2.143.
12. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172(10):1253-8. doi: 10.1164/rccm.200504-525OC.
13. Hossny E, Rosario N, Lee BW, Singh M, El-Ghoneimy D, Soh JY, et al. The use of inhaled corticosteroids in pediatric asthma: update. World Allergy Organ J. 2016;9:26. doi: 10.1186/s40413-016-0117-0.
14. Castro-Rodriguez JA, Custovic A, Ducharme FM. Treatment of asthma in young children: evidence-based recommendations. Asthma Res Pract. 2016;2:5. doi: 10.1186/s40733-016-0020-z.
15. Shin J, Oh SJ, Petigara T, Tunceli K, Urdaneta E, Navaratnam P, et al. Comparative effectiveness of budesonide inhalation suspension and montelukast in children with mild asthma in Korea. J Asthma. 2020;57(12):1354-64. doi: 10.1080/02770903.2019.1648504.
16. Nagao M, Ikeda M, Fukuda N, Habukawa C, Kitamura T, Katsunuma T, et al. Early control treatment with montelukast in preschool children with asthma: a randomized controlled trial. Allergol Int. 2018;67(1):72-8. doi: 10.1016/j.alit.2017.04.008.
17. Scaparrotta A, Di Pillo S, Attanasi M, Rapino D, Cingolani A, Consilvio NP, et al. Montelukast versus inhaled corticosteroids in the management of pediatric mild persistent asthma. Multidiscip Respir Med. 2012;7(1):13. doi: 10.1186/2049-6958-7-13.
18. 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. doi: 10.1164/rccm.200510-1546OC.
19. Walia M, Lodha R, Kabra SK. Montelukast in pediatric asthma management. Indian J Pediatr. 2006;73(4):275-82. doi: 10.1007/bf02825818.