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The Effect of Oral Montelukast in Controlling Asthma Attacks in Children: A Randomized Double-blind Placebo Control Study

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ABSTRACT

Oral Montelukast is recommended as maintenance therapy for persistent asthma, but there is controversy regarding its effectiveness in controlling asthma attacks. The present study was conducted to investigate the clinical efficacy of oral Montelukast for asthma attacks in children.

This study was conducted as a double-blind placebo-controlled clinical trial on 80 children aged 1-14 years with asthma who were admitted to the emergency department of Bahrami Children's Hospital (Tehran, Iran) during one year. Patients were randomly divided into case and control groups. In addition to the standard asthma attack treatment, Montelukast was prescribed in the case group and placebo in the control group for one week. Patients were evaluated in terms of asthma attack severity score and oxygen saturation percentage (SpO2) in room air as primary outcomes 1, 4, 8, 24 and 48 hours after admission.

In the first 48 hours, there was no significant difference in the score of asthma attack severity and SpO2 between the case and control groups. There was no significant difference between the groups in terms of length of hospitalization or number of admissions to the intensive care unit. None of the patients were re-hospitalized after discharge.

The results of this study showed that the use of Montelukast along with the standard treatment of asthma attacks in children has no added benefit.

Keywords: Asthma attack; Children; Montelukast

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INTRODUCTION

Asthma is known as the most common chronic childhood disease and the main cause of frequent hospitalizations as well as absences from school. The global prevalence of parent-reported, physician-diagnosed asthma in 6-7-year-old and 13-14-year-old children is estimated to be 10.8% and 13.8%, respectively.[1-3] Childhood asthma is considered a global epidemic, resulting in significant morbidity and mortality, especially in low- and middle-income countries.[4] Asthma manifests as a clinical syndrome including coughing, wheezing, shortness of breath, and chest tightness that changes in severity at different times.[5] This marked heterogeneity of phenotypes is attributed to different endotypes due to complex interactions between atopy, infections, hormones, diet, and genetic susceptibility.[6-8] Childhood asthma usually presents with an allergic phenotype characterized by the T helper lymphocyte type 2 (Th2) immune response.[9-11]

Leukotrienes, including cysteinyl Leukotrienes (CysLTs) and Leukotriene B_4, play a major role in the pathophysiology of asthma by mediating bronchoconstriction, vascular permeability, mucus hypersecretion, recruitment of inflammatory cells, and airway remodeling.[12] The effects of CysLTs are mainly exerted through CysLT type 1 (CysLT1) receptors, and therefore, these effects can be reduced by leukotriene receptor antagonists (LTRAs), including Montelukast, Pranelukast, and Zafirlukast..[13] Montelukast is the most prescribed LTRAs in the management of asthma.[14]

Although low-dose inhaled corticosteroid (ICS) together with an as-needed short-acting beta-2-agonist (SABA) have been classically recommended as the gold standard for management of long-term childhood asthma, international guidelines recommend LTRAs either as second-choice monotherapy or as add-on therapy to ICS.[15] Montelukast has been associated with a significant reduction in the rate of asthma exacerbations in children with intermittent or mild persistent asthma.[16.17] Montelukast may potentially be used in acute asthma attacks, as it has been shown to have acute bronchodilator effects.[18] The data regarding the use of Montelukast in acute asthma attacks in children are limited and the few studies have reported conflicting results.[19. 20] The present study was conducted to investigate the clinical efficacy of oral Montelukast in acute asthma attacks in 1-14-year-old children.

MATERIALS AND METHODS

Study Setting and Subjects

This randomized, double-blind, placebo -controlled trial was conducted in Bahrami Children Hospital, affiliated with Tehran University of Medical Sciences, Tehran, Iran, between January 2020 and January 2021.

Inclusion criteria: children aged 1-14 years referred to the emergency department with the diagnosis of asthma attack and symptoms of shortness of breath, wheezing or respiratory distress.

Exclusion criteria: diagnosis other than asthma, such as bronchiolitis or pneumonia, history of receiving leukotriene antagonists or oral corticosteroids within 10 days before consulting, or having a pre-existing medical condition (e.g. cystic fibrosis, feeding difficulty, and chronic lung disease). Patients whose parents did not consent and patients with very severe exacerbations who threaten respiratory arrest were also excluded.

Randomization and Blinding

A total of 80 children were randomly assigned in a 1:1 ratio via a permuted block schedule (size ten) to one of the two study groups. Clinical investigators and parents were blinded to the assignment groups.

Study Protocol

At presentation, all patients underwent a thorough clinical assessment. Demographic characteristics, signs and symptoms at the time of admission, past medical history (e.g., physician-confirmed asthma, other allergic diseases, and recent respiratory infections), oxygen saturation percentage (SpO2) at room air, and asthma severity on arrival were recorded. The asthma attack severity score (AASS) was calculated based on the criteria in Table 1. Each of the items in the first column (mild attack) was given a score of 1, in the second column (moderate attack) a score of 2 and in the third column (severe attack) a score of 3.

Table 1. Asthma attack severity scoring

Attack severity	Mild	Moderate	Severe	Threaten to respiratory arrest (were excluded)
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Breathlessness (Position in bed)	Can lie down	Prefers sitting	Sits upright	lies down with drowsiness
Talks in	Sentences	Phrases	Words	Cannot talk(Drowsy)
Wheezing	End expiratory	Pan Expiratory	Expiratory & inspiratory	No Wheezing
Use of accessory muscle	Usually not	Commonly	Usually	Paradoxical Thoracoabdominal movement
Respiratory rate	< +30% *	30-50% *	> +50% *	> +50%* or Grasping /apnostic
Pulse rate	<100	100-120	>120	Bradycardia
SpO2 (in room air)	>95%	90-95%	<90%	<90%

* Percentage increase in the respiratory rate compared to the normal upper limit for patient age
SpO2= Oxygen saturation percentage

The enrolled patients were randomly divided into case and control groups. In addition to starting the standard asthma attack treatment, according to the severity of the attack in both groups, chewable Montelukast was given to the case group [Airokast, Dr. Abidi Pharmaceuticals, Iran]. The dose of Montelukast was 4 mg once daily in children aged 1-5 years and 5 mg once daily in children aged 6-14 years old. Children in the control group received standard therapy along with placebo (chewable tablets of the same size, color, and taste as the Montelukast tablets; prepared by Dr. Abidi Pharmaceuticals, Iran).

After the initiation of treatment, the patients were assessed at 1, 4, 8, 24 and 48 hours. The primary outcome was the asthma attack severity score and Spo2 at room air and the secondary outcome was the duration of hospitalization and the number of patients admitted to the Intensive Care Unit (ICU). At the time of hospital discharge, patients in both groups were advised to continue treatment and return to the asthma and allergy clinic for a final evaluation after one week.

Statistical Analysis

The statistical analysis of the data was done using SPSS version 22 software. The clinical outcome data were analyzed using an “intention to treat" approach, and the baseline values of patients were randomized during the trial. For differences between the groups, categorical data were undertaken using Fisher exact tests, and t tests were used for continuous data. The analysis was conducted by a study statistician who was blinded to the study groups. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 80 patients [62.5% male (n=50), age range 1-14 years] completed the study. Of these, about 44% (n=35) were included in the case group and 56% (n=45) in the control group. The study design is shown in Figure 1. There was no significant difference between the groups in terms of demographic characteristics and clinical variables at the initial visit. Seventy-one patients (89%) were admitted to the pediatric ward and nine to the ICU. There was no significant difference between the groups in terms of hospitalization in the ICU (p>0.05). Also, none of the patients were re-hospitalized after discharge.

In the first 48 hours, there was no statistically significant difference in the Asthma Attack Severity Score (AASS) between the groups (p>0.05) (Figure 2). Also, during this period, there was no significant difference in the percentage of SpO2 between the groups. The duration of hospitalization was between 1 and 7 days, and no significant difference was observed between the groups in terms of the number of hospitalization days (p>0.05) (Figure 3).

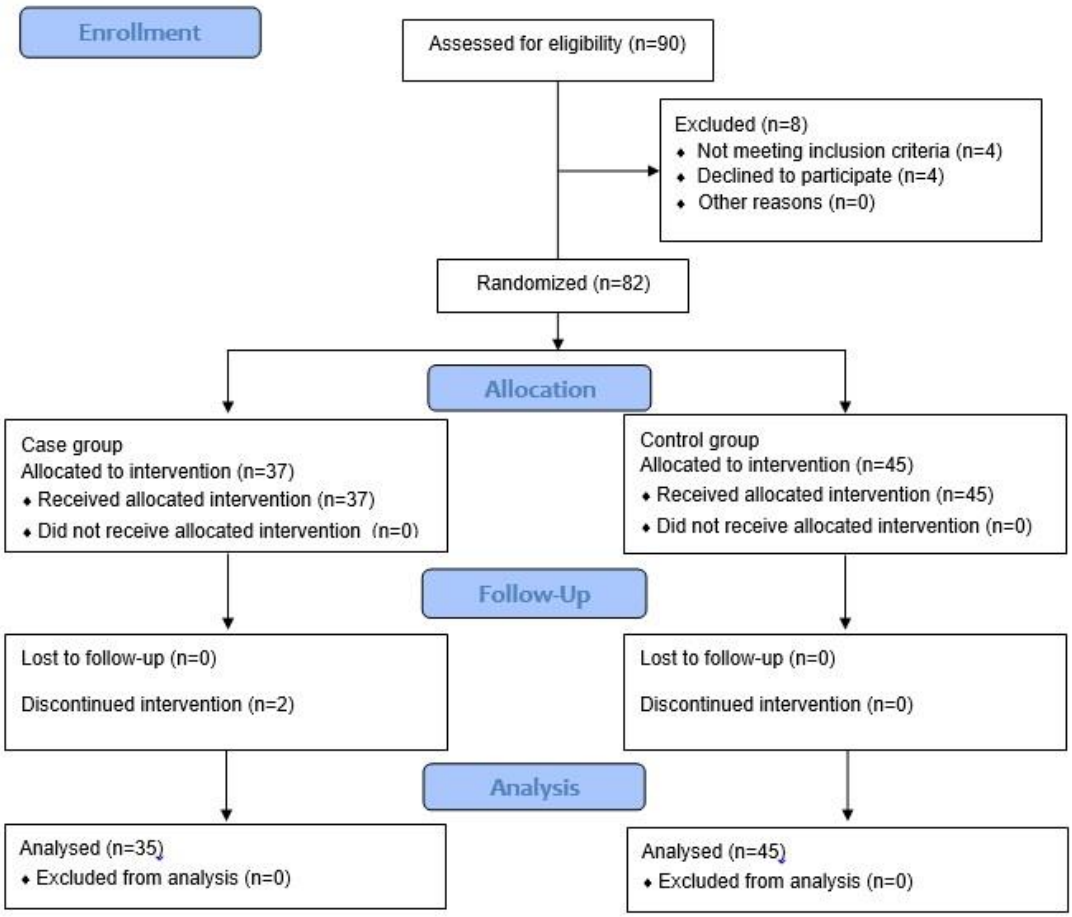

Figure 1. The study design chart (Consolidated Standards of Reporting Trials = CONSORT)

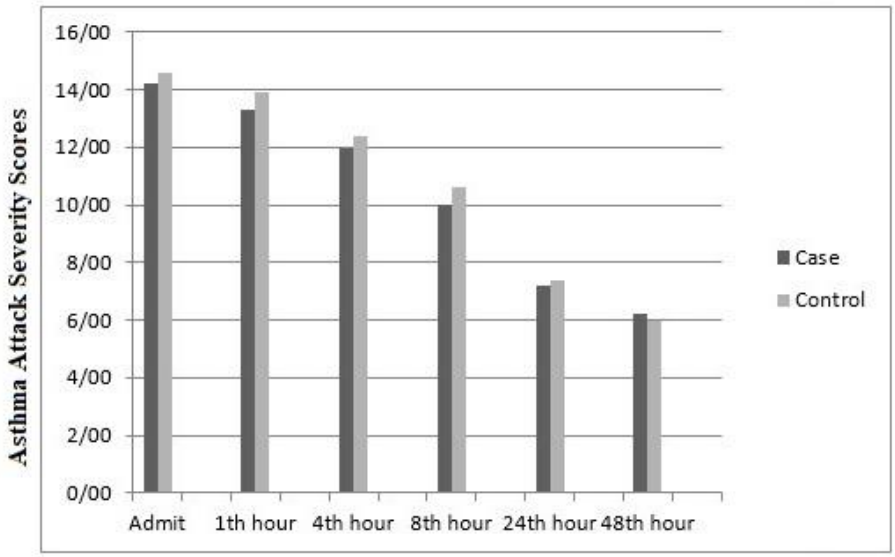

Figure 2. Comparison of asthma attack severity scores (AAST) between two groups from the time of admission to 48 hours later (n=40 in each group) There was no statistically significant difference between the groups (p>0.05)

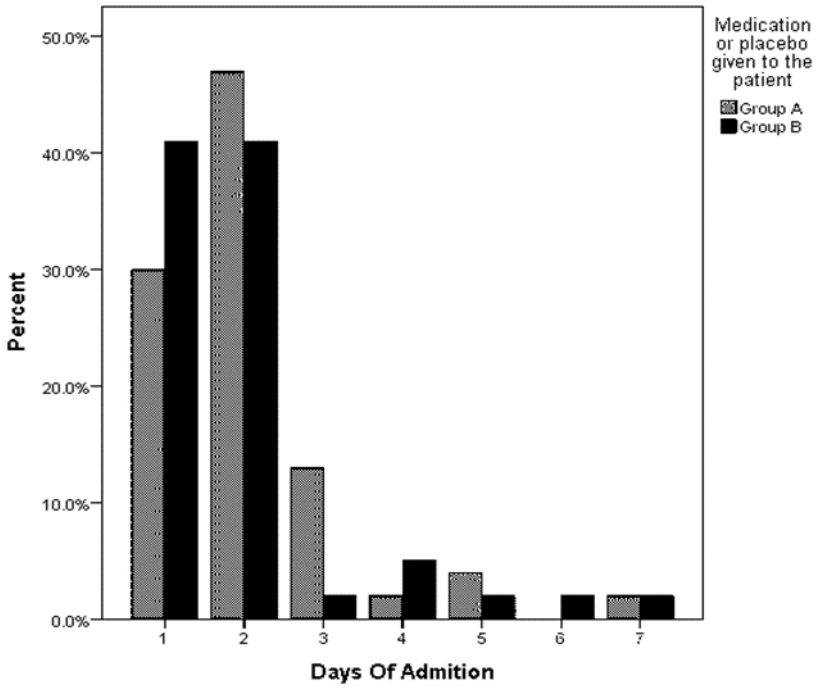

Figure 3. Comparison of hospitalization duration in two groups (group A: Montelukast, group B: placebo) There was no statistically significant difference between the groups (p>0.05)

DISCUSSION

In this study, we evaluated the clinical efficacy of adding oral Montelukast to standard asthma attack therapy in children aged 1-14 years. According to the results of our study, clinical improvement was observed in both the case and control groups. However, there was no significant statistical difference between the groups in terms of primary endpoints (i.e., asthma attack severity score and SpO2), and secondary endpoints (length of hospitalization, and number of patients hospitalized in the ICU).

In order to justify the non-significant difference between the groups, it can be pointed out that the prescription of standard asthma attack treatment could have masked the effect of Montelukast in the case group. Therefore, it seems that by increasing the number of study samples, the possibility of significant effectiveness of Montelukast would be evident.

Another possible explanation could be that oral Montelukast was not effective in managing asthma attacks, and any observed effectiveness may have been attributed to the use of alternative medications.

Two clinical trial studies conducted by Wang et al,[19] in children and Magazine et al,[21] in adults assessed the efficacy of Montelukast when added to the standard treatment for asthma attacks. In both studies, Montelukast was no more effective than placebo in increasing peak expiratory flow rate (PEFR) during hospitalization and at discharge. Similarly, forced expiratory volume in the first second (FEV1) at discharge did not show a significant difference between the two groups. The results of these studies are consistent with ours.

According to the study by Harmanci et al, compared with placebo, a single dose of Montelukast in children with a clinical history of intermittent asthma who were experiencing mild to moderate asthma exacerbations significantly reduced pulmonary index scores and respiratory rate.[20] The reason for the different results of the Harmasi study from ours could be that we did not classify the patients into intermittent and persistent types based on the severity of asthma and included all patients with any severity of asthma. It is possible that if our study was conducted on a larger sample size and the patients were classified into different subgroups,

including different severity of asthma, the effect of Montelukast would be revealed in some subgroups.

In the study by Chaudhury et al, the effectiveness of oral Montelukast on 160 adult patients with asthma exacerbations was evaluated by lung function tests. The results of that study showed a significant increase in FEV1 in 4 weeks and PEFR in 2 weeks and 4 weeks.[18] The difference between the results of Chaudhury's study and ours can be due to the difference in the study population (age of patients).

In the studies of Wang [19]and Chowdhury[19], the effectiveness of Montelukast in asthma attacks has been evaluated by pulmonary function tests. In contrast, in our study, assessment was based on clinical criteria, and it is possible that similar results would have been obtained if pulmonary function tests had been assessed.

The results of this study showed that adding Montelukast to the standard treatment of asthma attacks in hospitalized children has no added benefit.

This study has some limitations. Biological markers such as cysteinyl leukotriene level, which has been shown to increase in asthma attacks, were not measured.[22] Also, pulmonary function tests were not evaluated. This study was a single-center study and therefore it cannot be generalized to the entire population of children. In addition, the sample size is a considerable limitation which needs to be resolved in the future studies.

We have some suggestions for future studies such as evaluating the role of oral Montelukast in the treatment of asthma attacks, multicenter trials with larger sample sizes and evaluation of non-clinical indicators such as biological markers and pulmonary function tests. It is also recommended to classify patients into different subgroups in terms of clinical characteristics (such as severity of asthma, atopy, etc.) in future studies. Since, according to some studies, intravenous Montelukast has been effective in the treatment of asthma attacks, which may be due to the faster effect of the intravenous form than oral, it is suggested to compare the effect of intravenous and oral Montelukast on asthma attacks in future studies.

STATEMENT OF ETHICS

The patient's parents or guardians signed the written informed consent form before enrollment. Patients could withdraw from the study at any time. Patient information remained confidential. This study was conducted in accordance with the Declaration of Helsinki and international principles governing clinical research. Also, no extra cost was imposed and the cost of the drug and placebo was financed by the researcher. This study was registered in the Iranian Clinical Trials Registry (ID: IRCT20200412047048N1) and approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1397.098).

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There were no supporting source for the study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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