



Short Communication

Efficacy of Montelukast for Prevention of Upper Respiratory Tract Infection in Children: A Randomized, Placebo-Controlled Trial

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Article Info

Article History:

Received: 25 August 2019

Accepted: 1 January 2020

ePublished: 27 June 2020

Keywords:

-Upper respiratory tract infection
-Montelukast
-Children
-Fever

Abstract

Background: Upper Respiratory tract infection (URTI) or common cold is very prevalent in children particularly in young children. Leukotriene receptor antagonists (LTRAs) like montelukast are effective drugs in asthma and some other respiratory diseases. Our purpose was to study preventive effects of montelukast on pediatric URTI.

Methods: This randomized, placebo-controlled, and double blind trial was performed on 450 healthy children aged 1-5 year in Amir Kabir Hospital, Arak, Iran. Children were randomized 1:1 to placebo group or montelukast group for 12 weeks. Number of URTI episodes and duration were the primary end points and were compared at baseline and after termination of treatment.

Results: Mean age was 28 ± 12.3 months. Mean of URTI episodes was 0.7 ± 0.57 in children treated with montelukast and 1.27 ± 0.72 in children treated with placebo, respectively. Differences were statistically significant ($P = 0.01$). A significant difference was seen in URTI duration between two study groups (6.3 ± 6.1 vs 4.1 ± 3.9 , $P = 0.05$). In addition, duration of fever was shorter in children receiving montelukast ($P = 0.001$).

Conclusion: Our study indicates that 3 month treatment with montelukast is effective for reducing the incidence of URTI in young children. This treatment has an acceptable safety without any serious concern.

Introduction

Upper Respiratory tract infection (URTI) or common cold is one of the most prevalent problems in children. It has usually a higher incidence rate in children younger than 5 years.^{1,2}

URTI is usually the main cause of hospital admission and missed days at work or kindergarten. Of note, it has a high cost to the society. Ear infection, sinusitis, and exacerbations of reactive airway diseases are important complications of URTI.¹⁻³ Noteworthy, there is no specific treatment for pediatric URTI. Many viruses and bacteria are involved in the pathogenesis of URTI, therefore it is difficult to have a single vaccine which can prevent the occurrence of childhood URTI.⁴ In many cases, URTI is self-diagnosed and self-treated and supportive therapies can solve the problem. However, in cases with high fever and serious infections antibiotics are ordered.^{4,5} Leukotrienes have a pivotal role in the initiation and development of some inflammatory reactions including URTI. They are involved in congestion, bronchoconstriction,

and bronchospasm.⁶ They can be suppressed through two ways; inhibition of lipoxygenase which is involved in the production of leukotrienes and blockade of its receptor.

Leukotriene receptor antagonists (LTRAs) like montelukast and zafirlukast have well established effects for prevention and treatment of asthma in children. In addition, they have pediatric application in exercise-induced bronchospasm and allergic rhinitis.^{7,8}

Montelukast is approved in children older than 12 months. It is generally well tolerated and shows many positive effects in asthmatic patients.^{9,10} Headache and mild gastrointestinal upset are frequent side effects of montelukast.¹¹ Due to presence of leukotrienes in URTI, it is expected that LTRAs can offer therapeutic benefits. Till now, limited studies have provided evidence for effects of montelukast in URTI and present data are uncertain. We aimed at assessing the prophylactic role of montelukast on childhood URTI.

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Materials and Methods

Study design

The study was performed in Amir-Kabir Hospital, Arak, Iran. Four hundred and fifty healthy children aged 1-5 years were included. The study was done between August 2017 and May 2018. Participants were excluded if they had acute or chronic air-way disease, active URTI, use of bronchodilators, use of corticosteroids and montelukast, history of hypersensitivity, seasonal or allergic rhinitis, and chronic heart disease. Sealed envelopes with an enclosed assignment were used for allocation concealment. Four hundred and fifty individuals were calculated with the assumption of 15% dropout in number of the subjects for detection of differences in URTI duration and URTI episode. The power was 80%. This was a randomized, placebo-controlled, and single center study. We used simple randomization method. All participants and caregivers were masked. Subjects were randomized 1:1 to oral 5 mg/day montelukast or placebo for 12 weeks. They were asked to have the drug or placebo in the morning.

Efficacy measures

Number of URTI episodes and URTI duration were the primary end points. Sneezing, coughing, nasal congestion, and fever (body temperature $> 37.3^{\circ}\text{C}$, axillary) were suggestive for URTI if subjects had at least 2 symptoms.¹² URTI duration was measured at diagnosis day until the day which all symptoms were resolved. Parents were trained for symptoms of URTI and they were asked to record number and duration of URTI episodes. Secondary outcomes were adverse effects of drugs, use of antibiotics and antipyretics, and absence from kindergarten.

Safety measures

Physical examination was done at baseline and every month by physician. Subjects were visited monthly for 3 months. For assessment of side effects of the drugs, participants were monitored weekly by phone for any systemic upset and hypersensitivity. Parents were trained for possible adverse effects of montelukast and were asked to call the clinic immediately in case of any problem.

Data analysis

Kolmogorov–Smirnov was used to test normal distribution of data. Student t test, Mann–Whitney tests, χ^2 test, and Fisher's exact were used for data analysis. $P < 0.05$ was considered as statistical significance. Analysis was performed using SPSS software version 21.0.

Results

Of the 450 individuals who were included 70 children did not receive the treatments (27 did not use the medications, and 21 met the exclusion criteria). Twenty two children were lost to follow up and 380 participants had complete observation over the course of 3 months. Table 1 shows baseline characteristics of subjects. The mean age was 28 ± 12.3 months with an excess of males (58%). At baseline, no significant differences were noted in children's characteristics. Flow diagram for study participants is shown in Figure 1. For possible confounding factors, birth order (first birth or not), number of family member (less than or equal to four), number of rooms in the house, and number of sibling (less than or equal to one) were analyzed. Confounding factors were equally distributed between the two groups ($P > 0.05$). As shown in Table 2, the reported mean number of URTI episodes was 0.7 ± 0.57 in children treated with montelukast and 1.27 ± 0.72 in children treated with placebo. The between group differences were statistically significant ($P = 0.001$). URTI duration was significantly shorter in montelukast group (4.1 ± 3.9 (day) vs 6.3 ± 6.1 (day), $P = 0.05$). Frequency of fever was 63.5 % in montelukast group and 86.8 % in placebo group ($P = 0.001$). In addition, duration of fever was significantly shorter in montelukast group (2.7 ± 2.4 day) compared with placebo group (4.84 ± 2.86 day, $P = 0.001$). There were significant differences in use of antibiotics and antipyretics between two study groups ($P < 0.05$). Frequency of antibiotic use was 14 % in montelukast group and 25 % in placebo group; the between group difference were statistically significant ($P = 0.007$). Moreover, frequency of antipyretics use was significantly higher in children who received placebo ($P = 0.001$). Rhinitis and cough had higher rate of incidence in the placebo group ($P = 0.05$). The incidence of otitis, pneumonia, and pharyngitis was similar in both groups ($P > 0.05$) and the mean number of outpatient

Table 1. Baseline characteristics of participants. Data are shown as mean \pm SD and number (%).

Characteristics		Montelukast group (n=190)	Placebo group (n=190)	P
Age, month		29.53 \pm 13.29	27.04 \pm 11.95	0.05
Male		100 (52.6%)	120 (63.2%)	0.07
Parental smoking		70 (36.7%)	72(37.4%)	0.80
Previous hospitalization		85 (45.3%)	93 (49.5%)	0.67
N of rooms in the house	Less than two	138 (72.6%)	142 (74.7%)	0.62
	More than two	52 (27.4%)	48 (25.3%)	0.80
N of family members	Less than four	139 (73.2%)	139 (73.2%)	1.00
	More than four	51 (26.8%)	51 (26.8%)	0.90
Birth order	First birth	71 (37.4%)	57 (30%)	0.13
	Second birth or above	119 (62.6%)	133 (70%)	0.22
Sibling	One and less than one	137 (72.1%)	139 (73.2%)	0.80
	More than one	53 (27.9%)	51 (26.8%)	0.61

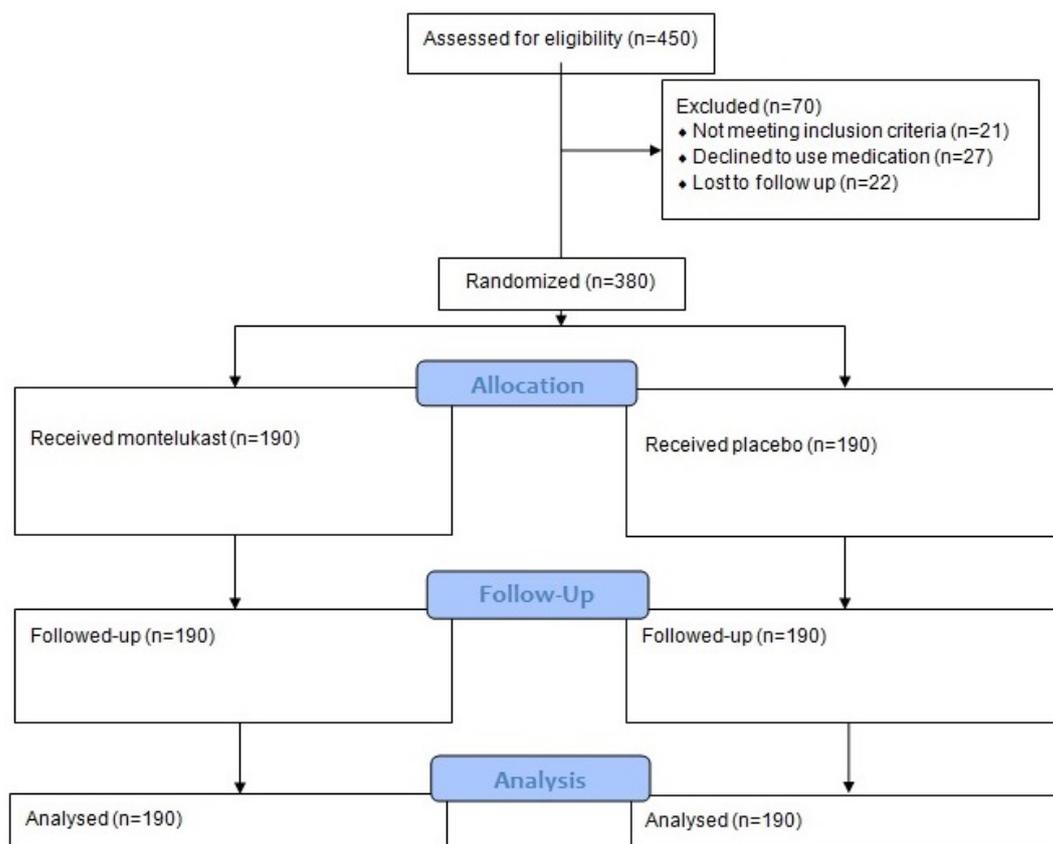


Figure 1. Consort diagram detailing study subjects.

Table 2. Effects of treatments on study endpoints. Data are shown as mean \pm SD and number (%)

Characteristics	Montelukast group (n=190)	Placebo group (n=190)	P
Number of URTI episode	0.7 \pm 0.5	1.2 \pm 0.7	0.001
Average duration of URTI (day)	4.1 \pm 3.9	6.3 \pm 6.1	0.05
Absence from kindergarten	19 (10%)	24 (13.2%)	0.26
Parent missed works	38 (21.1%)	66 (35.3%)	0.001
Frequency of adverse effects	0	0	1.00
Fever	120 (63.5%)	163 (86.8%)	0.001
Cough	112 (59.5%)	146 (77.4%)	0.001
Unscheduled visits	121 (64.2%)	43 (86.8%)	0.001
Number of outpatient visit	0.69 \pm 0.54	1.26 \pm 0.72	0.001
Incidence of otitis	4 (28.6%)	10 (71.4%)	0.10
Incidence of pneumonia	12 (40%)	18 (60%)	0.25
Incidence of pharyngitis	11 (33.3%)	22 (66.7%)	0.04
Hospitalization	12 (38.7%)	19 (61.3%)	0.19

visit was statistically higher in placebo group ($P=0.001$). However, there were no differences in the frequency of hospitalization in study groups ($P=0.19$).

Discussion

This randomized and placebo-controlled trial showed that 3 month treatment with montelukast is effective for reducing the incidence of URTI in young children. This study confirmed that montelukast significantly reduced URTI episodes and URTI duration. Upper respiratory tract infection (URTI) or common cold is one of the most prevalent diseases and is a leading reason for unscheduled

outpatient visits in adults and in children.^{1,13} Children particularly preschool children may experience URTI up to 6-10 times per year.¹⁴ Many viruses are associated with nasal discharge, cough, nasal congestion, sore throat, sneezing, lower respiratory infection, and otitis media. URTI has a high cost to society and is usually associated with kindergarten absence and missed days at works for parents.⁴ The leukotrienes exhibit a number of biological effects such as attraction and activation of leukocytes, contraction of bronchial smooth muscles, and stimulation of vascular permeability.¹⁵ Some studies have shown that in infants with respiratory syncytial virus (RSV)

bronchiolitis, levels of leukotriene C4 in nasal lavage fluid were significantly higher than healthy controls, which persisted after one month of acute infection.¹⁶ Moreover, an increase in leukotriene 4 levels in nasal secretions and a relationship between symptoms and leukotriene levels have been reported in experimental models of infection by influenza A, rhinovirus, and RSV.^{17,18} Many investigations have assessed the role of montelukast in respiratory problems such as chronic asthma, seasonal allergic rhinitis, mild asthma, and respiratory syncytial virus post-bronchiolitis. A work by Yoshihara showed that LTRAs like montelukast can reduce asthma attacks in response of common cold in young children.¹⁹ A study demonstrated that 8 weeks treatment with montelukast is able to improve asthmatic status in children with no serious concern.²⁰ Another work by Bisgaard proved that 28 days treatment with montelukast lead to disease improvement in infants between 3 to 36 months of age diagnosed with bronchiolitis.²¹ To our knowledge, till now one study has investigated the role of montelukast in URTI. A work by Kozer et al showed that 3 month treatment with 4 mg montelukast is not associated with reduction in URTI frequency and duration in preschool-aged children.²² Compared to our study, they investigated different variables with a smaller sample size. However, they reported no benefits for preventive role of montelukast on URTI frequency and duration. Interestingly, Kozer's study showed that montelukast use was associated with an increase in fever and in use of antibiotics. Like the mentioned work, we found no significant difference in the incidence of otitis in both study groups. Differences in number of family members, exposure to smoking, and lower socioeconomic profiles may partially explain the opposite findings. Leukotrienes can facilitate the migration of other inflammatory players by process which is known as chemotaxis.²³ Montelukast blocks binding of leukotriene to its receptor and hence interrupts inflammatory responses. Montelukast is available in tablet and oral granules. It has rapid oral absorption. The half-life is about 3-6 hours and it is chiefly cleared by the liver.²⁴ In the present work, a 3-month montelukast therapy had no serious adverse effects. In general, montelukast is well tolerated by adults and children. Headache, abdominal pain, rash, and dyspepsia are seen in 2-10 % of patients.²⁵ Of note, FDA reported some concerns about central effects of montelukast; restlessness, hallucination, agitation, sleep disorders, and suicide. However, the frequency of these adverse effects are not defined.²⁶ Till date, no serious interaction has been reported between montelukast and other drugs using for management of childhood URTI. The present study has a number of limitations. Our study was single center and our findings should be confirmed by multicenter trials. Of note, we did not assess the chronic effects of montelukast administration and we could not measure levels of leukotrienes in subjects with URTI. Our data was collected from parents' records; therefore the level of compliance is not very clear and there has

been no verification. Moreover, it is likely that our studied endpoints and drug effects have some errors. There is a sound rationale for further trials with greater statistical power among children of this age.

Conclusion

Our study indicates that 3 month treatment with montelukast is effective for reducing the incidence of URTI in young children. This treatment has an acceptable safety without any serious concern.

Ethical Issues

Ethics Committee of Arak University of Medical Sciences university (ethical code:91-128-13) approved the study and written informed consent was taken from or parent(s) or by the legal representative prior to trial participation. The clinical trial registry number was IRCT2012103111339N1. Participants were discontinued from the study for these reasons: safety; any severe adverse effects to treatments or concomitant diseases, lost to follow-up, and voluntary discontinuation.

Data Sharing

Applicants can obtain data by contacting the corresponding author.

Acknowledgments

This study was supported with a grant of vice chancellor of research of Arak University of Medical Sciences (grant no. 796). The authors are thankful to staff of Amir Kabir Hospital for their assistances with this project.

Conflict of Interests

The authors declare that they have no conflict of interest.

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