The Effects of Montelukast in Children Between 6-16 Years with Moderate-Severe Acute Asthma Attack

Orta-Ağır Akut Astım Atağı ile Başvuran 6-16 Yaş arası Çocuklarda Montelukastın Etkinliğinin Belirlenmesi

[1]Beyhan Küçükbayrak, [2]Koray Harmancı, [3]Gülşen Köse, [2]Hülya Anıl
[1]Clinic of Pediatrics, Izzet State Hospital, Bolu, Turkey
[2]Pediatric Allergy and Immunology Department, Osmangazi University Medical Faculty, Eskisehir, Turkey
[3]Neurology Department, Sisli Etfal Training and Research Hospital, Istanbul, Turkey

Abstract: The aim of this study is to evaluate the effect to respiratory parameters (retraction, asthma attack score-AAS, positive expiratory flow rate- PEFR-, dispnea parameters, auscultation) of montelukast in children aged between 6-16 years admitted with moderate or severe acute asthma attacks. In this study, thirty children presented with moderate or severe asthma attack were evaluated. The study is a randomized, double blind, placebo-controlled parallel trial. The patients were randomly divided into two groups. All patients were given nebulized salbutamol (0.15 mg/kg), ipratropium bromide (250 mcg/doz), 1 mg/kg of oral methyl prednisolone and O2 as initial treatment. In addition to these medications, the placebo of montelukast 5 mg was given orally in the Group I, and montelukast 5 mg drug was given orally to the patients in the Group II. Then, additional 0.15 mg/kg nebulized Salbutamol and 250 mcg/dosage Ipratropium bromides were given twice with 20 minute interval. Besides, the patients were evaluated at 0., 20., 40., 60., 90., 120., 180., and 240. minutes for the criteria of therapeutic response such as respiratory parameters. The mean age of children in the study group was 9 (between 6.5-16), male to female ration (M/F) was 1. In the first group, mean age 9.5, M/F:0.87. Median age was 9 and (M/F) was 1.14 in Group II. No significant difference was determined between groups in terms of respiratory parameters. Nevertheless, the average rate of improvements in the respiratory parameters in group II was higher than group I. The rates of improvement in the average scores at every evaluation times were higher in the group II in comparison with the group I. However, the differences between the groups at every evaluation time were not significant statistically ($p>0.05$). The use of montelukast in children aged between 6-16 years with acute asthma exacerbation seems to be effective in improvement of respiratory parameters, especially in PEFR and AAS.
Key Words: acute asthma, anti-asthmatic agents, children, montelukast.

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Özet: Bu çalışmanın amacı orta veya ağır şiddette astım atağı ile başvuran 6-16 yaşlar arasındaki hastalardaki solunum parametrelerine (retraksiyon, astım atak skoru, pozitif ekspirasyon akış hızı, dispne parametreleri, oskültasyon bulguları) montelukastın etkisini araştırmaktır. Çalışmamıza orta ve ağır şiddette akut astım atağı ile başvuran 30 astımlı çocuk dahil edildi. Çalışma; randomize, çift kör, plasebo kontrollü, paralel bir incelemedir. Tüm hastalara başlangıç tedavisi olarak nebulize salbutamol nebulized salbutamol (0.15 mg/kg), ipratropium bromid (250 mcg/doz), oral metilprednizolon (1 mg/kg) ve oksijen verildi. Bu tedavilere ek olarak Grup I'deki hastalara 5 mg plasebo, Grup II'dekilere montelukast 5 mg oral olarak verildi. Ardından her iki gruba da 20 dakika aralarla 2 kez daha 0,15 mg/kg nebulize salbutamol ile 250 mcg/doz nebulize ipratropium bromür verildi. Hastalar 0., 20., 40., 60., 90., 120., 180. ve 240. dakikalarda respiratuar parametrelerle tedavi etkinliği açısından tekrar değerlendirildi. Çalışmaya dahil edilen çocukların yaşları 6,5 ile 16 arasında değişmekte ve ortanca yaş 9, erkek kız oranı eşitti. Grup I'de hastaların median yaşı 9,5 yaş, erkek kız oranı 0.87 idi. Grup II'de hastaların median yaşı 9 yaş, erkek kız oranı 1.14 idi. Tedavi öncesi gruplar arasında çalışma parametreleri arasında anlamlı fark bulunmadı ($p > 0.05$). Bununla birlikte grup-II'deki ortalama solunum parametrelerindeki düzelme oranı grup-I'e göre daha yüksek bulundu. Grup II'deki hastaların astım atak skorlarındaki düzelme tüm dakikalarda diğer gruba göre daha yüksekken, aradaki fark istatistiksel olarak anlamlı değildi ($p > 0.05$). Montelukastın 6-16 yaş arası orta veya ağır şiddette astım atağı ile başvuran çocuklarda kullanımında PEFR'de ve astım atak skorlarının düzelmesinde etkili olduğu saptanmıştır.
Anahtar Kelimeler: akut astım, anti-astmatik ilaçlar, çocuklar, montelukast.

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Yazışma Adresi / Correspondence Address
Hülya ANIL
mail: hulyaanil26@gmail.com

1. Introduction

Asthma is a chronic inflammatory disease of respiratory tract. The incidence of this disease is approximately 10% in childhood and gradually increasing. In parallel to the increase in asthma incidence, the number of patients appealing to the emergency units or allergy policlinics because of acute asthma attack is also increasing (1,2). The first step prior to initiating the therapy must be the designation of the severity of attack. Hence, according to the international guideline for asthma diagnosis and management last published in 2009 by Global Initiative for Asthma (GINA), the patients are classified in 4 distinct groups from mild to life-threatening attack severity and the treatment is planned for the corresponding group (3)

Anti-leukotriene drugs are used safely in chronic asthma treatment since their anti-inflammatory properties do not begin immediately (4-6). These drugs are divided into two groups, leukotriene receptor antagonists and 5-lipoxygenase inhibitors. The leukotriene receptor antagonists act via binding to cysteinyl leukotriene-1 receptor and montelukast is in this group (7). Montelukast is preferred because of its bronchodilator and anti-inflammatory effects, being able to control singly asthma and allergic rhinitis symptoms, lack of known severe adverse effects, no need to adjust its dose in case of renal failure and mild-moderate hepatic failure, suitability for children over 7 years, single dose regimen, lack of interaction with food and warfarin (8). Anti-leukotrienes are recommended as a first choice for chronic monotherapy in the treatment of mild persistent asthma to prevent attacks, it is accepted that with the use of these drugs in addition to corticosteroids (CS), the course of asthma is affected positively in advanced clinical pictures, and CS dose can be reduced (9). Moreover, recent studies demonstrated that single dose oral montelukast (leukotriene receptor antagonist) provided remarkable improvement in pulmonary function tests in asthma patients (10). Montelukast establishes its effect tardy, so that it is not among first-line options for the treatment of the patients presenting with acute asthma attack.

In this study, all pediatric patients aged between 6-16 years, who appyled to the pediatric emergency unit and allergy policlinic because of moderate or severe asthma attack were given short-acting β-2 agonist, ipratropium bromide, O_2 and systemic methyl prednisolone. In addition to the medications stated above, one-half of the patients were given orally 5 mg of montelukast, a leukotriene receptor antagonist, the remaining half of the patients were given placebo of this drug. So that the efficacy of montelukast in the treatment of acute asthma attacks was ascertained.

2. Materials and Method

This study included 30 children with moderate and severe acute asthma attack, who appealed to the pediatric emergency unit and allergy policlinics in the Ankara Child's Health and Disorders Hematology and Oncology Training and Research Hospital. The ethics committee of the hospital approved this research.

The study is a randomized, double blind, placebo-controlled parallel trial. The patients were randomly divided into two groups. All patients were given nebulized salbutamol and ipratropium bromide, 1 mg/kg of oral methyl prednisolone and O_2 as initial treatment. In addition to these medications, the placebo of montelukast 5 mg was given orally in the Group I, whilst montelukast 5 mg drug was given orally to the patients in the Group II.

Anamneses of all patients were questioned, their systemic examination was done, and oxygen saturation was determined using oximetry. The study included the patients who had an asthma attack score (AAS) <11 or a peak expiratory flow rate (PEFR) >50, which was measured with peak flowmeter and those who had used inhaler corticosteroid drugs and had a stabile drug dose throughout 2 weeks prior to the study period.

At the time of admission in our clinics, we excluded those patients meeting following criteria: taking corticosteroids within the last

one month; high-dose inhaler corticosteroid use within the last 2 weeks; the use of theophylline, nedocromil, cromolyn sodium or inhaled anticholinergics within the last 2 weeks; receiving a long-acting β-2 mimetic 24 hours before the study, a short-acting antihistaminic 48 hours before the study or a long-acting antihistaminic 2 weeks before; having chronic lung disease or any other systemic disease; presence of an inferior respiratory tract disease other than asthma.

During the study, it was planned to exclude the patients having any of following: development of a drug-induced severe side effect; inability to administer the drug because of any reason; exacerbation of the patient's symptoms during the study; no response at the second hour of the study (severe respiratory distress, increase in heart and respiratory rates, PEFR <%50, sO2<91%, AAS≥12) and insufficient response at hour 4 of the study (moderate respiratory distress, increase in heart and respiratory rates, PEFR = %50-70, sO2 91-93% and AAS=8-11). There were no patient meeting these criteria, therefore, none of the patient was excluded from the study.

The study was conducted with totally 30 patients aged between 6,5 and 16 years (median age was 9 years). Of the patients, 15 (50%) were girls and 15 (50%) were boys. Fifteen patients (50%) included in the study were administered placebo treatment in addition to classical asthma attack management and this group of patients was called "Group I". the remaining 15 patients (50%) were given montelukast treatment in addition to classical asthma attack management and this group of patients was defined as "Group II". The median age was 9,5 years and boys/girls ratio was 7/8 in the Group I. In the Group II, the median age was 9 years and boys/girls ratio was 8/7.

In the group II, the patients were given salbutamol (0.15 mg/kg), ipratropium bromide (250 mcg/dose) and 5 mg oral formulation of montelukast together with the first dose of methyl prednisolone; then, further two doses of 0.15 mg/kg of nebulized salbutamol were given with 20-minute intervals and 250 mcg/dose of nebulized ipratropium bromide was given. The medications given in the group I were the same, except the placebo of montelukast as replacement for montelukast itself. After the ward nurse gave montelukast 5 mg drug or placebo to the child without notifying the physician, the syringes containing salbutamol and ipratropium bromide, which were prepared by the same nurse, were given to the physician. The maximum dose of salbutamol did not exceed 5 mg regardless of the body weight of the child. Methyl prednisolone was initiated with the dose of 1 mg per kilogram and maximum dose was designated to be 40 mg. The doses of the medications were assigned according to the GINA international guideline 2009 recommendations for children.

The two groups were compared in terms of demographic characteristics. Besides, the patients were evaluated at 0., 20., 40., 60., 90., 120., 180., and 240. minutes for the criteria of therapeutic response such as PEFR and asthma attack score. The AAS is comprised of suprasternal and scalene muscle retractions, air entry, wheezing, and oxygen saturation with a score range of 0 to 12 points, 12 being the greatest severity. Components of the AAS were recorded separately, and scores were calculated electronically.

Statistical Analysis

For the comparison between the groups, the independent samples t-test was used for data showing normal distribution, Mann-Whitney U-test was used for data not showing normal distribution. The significance was assigned by $p>0.05$.

3. Results

In the group I, the duration of symptoms was 1 to 10 days, the number of attacks within the last one year was 1 to 20, the number of admissions in the pediatric emergency unit ranged from 1 to 12. The corresponding values for the group II were 1 to 12 days, 1 to 20, and 0 to 24 (Table 1). Given allergic disease history and family medical history, upper respiratory tract infection was found in 9 patients from the group I and in 8 patients in the group II at the time of admission; atopy history was present in 7 patients each from the group I and group II; eczema history was present in 1 and 3 patients from the group I and group II, respectively; the family history of asthma was present in 12 and 5 patients and the family history of smoking was present in 8

and 9 patients from the group I and group II, respectively (Table 2).

Table-1.
Asthma features in the patients (min-max, mean and median values)

	Min-max		mean		median	
	Group-1	Group-2	Group-1	Group-2	Group-1	Group-2
The duration of symptom	1-10	1-12	2.60	3.14	2.00	2.00
Attacks number in late one year	1-20	1-20	3.66	8.84	2.00	3.00
Presented number to PER (in late one year)	1-12	0-24	2.40	5.84	1.00	2.00

PER: Pediatric emergency room

Table-2.
Allergic disease and family history in the patients

	Group-1		Group-2	
	Yes	No	Yes	No
Attack URTI	9	6	8	7
Atopy	7	8	7	8
Eczema	1	14	3	12
Asthma in parents	12	3	5	10
Smoking in parents	8	7	9	6

URTI: Upper respiratory tract infection

PEFR values of the patients at the time of admission were 133±74.73 in the group I and 136.66±79.72 in the group II (p>0.05). The scores at 90 minutes were 208.66±81.38 in the group I and 223.33±91.93 in the group II (p > 0.05). The scores at 240 minutes were 195.83±77.95 in the group I and 228.66±80.05 in the group II (p > 0.05). The rate of recovery was 67.64% in the group II and 46.48% in the group I at the end of 4 hours. Although there was no significant difference between the group I and group II in terms of PEFR scores for all minutes, the average PEFR score of the group II was found to be higher than that of the group I (Table 3).

Table-3.
The comparison of PEFR parameters in the patients.

	Group-1 (mean±std dev)	Group-2 (mean± std dev)	p
PEFR 0	133.00 ± 74.73	136.66± 79.72	>0.05
PEFR 20	178.00 ± 77.54	177.00 ±92.23	>0.05
PEFR 40	193.00 ± 85.33	201.78 ±103.28	>0.05
PEFR 60	201.66 ± 87.17	214.33 ±90.68	>0.05
PEFR 90	208.66 ± 81.38	223.33± 91.93	>0.05
PEFR 120	218.33 ± 83.82	227.00 ±90.92	>0.05
PEFR180	205.00 ± 80.46	225.66 ±79.66	>0.05
PEFR 240	195.83 ± 77.95	228.66± 80.05	>0.05

Grup-1: Classical therapy and plasebo

Grup-2: Classical therapy and montelukast
(Independent Samples t Test; p<0.05)
PEFR: Positive expiratory flow rate

At the time of admission, AAS was 10.46±2.19 in the group I and 10.69±1.70 in the group II (p > 0.05). AAS scores at 90 minutes were 7.76±1.55 and 7.61±1.85 for the group I and group II, respectively; these scores at 240. minutes were 7.08±2.02 and 6.55±1.50 for the group I and group II, respectively (p > 0.05). At the end of 4 hours, the asthma attack score declined by 38.72% in the group II and by 32.69% in the group I in comparison with the initial scores. The rates of improvement in the average scores at every evaluation times were higher in the group II in comparison with the group I. However, the differences between the groups at every evaluation time were not significant statistically (p>0.05) (Table 4).

Table-4.
Comparison of attack scores in the patients.

	Group-1 (mean±/-std dev)	Group-2 (mean±/- std dev)	p
Score 0	10.46 ±2.19	10.69± 1.70	>0.05
Score 20	9.33±1.95	9.23±1.69	>0.05
Score 40	8.93±2.15	8.76±1.16	>0.05
Score 60	8.26±2.12	7.92±1.49	>0.05
Score 90	7.86±1.55	7.61±1.85	>0.05
Score 120	7.60±1.72	7.23±1.69	>0.05
Score 180	7.30±1.65	7.00±1.61	>0.05
Score 240	7.08±2.02	6.55±1.50	>0.05

Group-1: The group of classical therapy and plasebo
Group-2: The group of classical therapy and montelukast
(Independent Samples t Test; p<0.05)

In the comparison of the group I and the group II in terms of respiratory parameters, no significant differences was found between the initial values and the values obtained throughout the evaluation period. However, the rates of improvement in the average values of respiratory parameters were higher in the group II in comparison with the group I. The severity of retraction was improved much better in the group II patients in comparison with the group I patients. However, this improvement was not found to be statistically significant (p>0.05). Given the auscultation and dyspnea parameters, the group II showed better improvement than the group I did, but the difference was not significant (p>0.05). There were not severe side effects that required interrupting the study in any patient of both groups.

At the end of 4-hour monitoring, all patients responded to the treatment and none of them required hospitalization.

4. Discussion

In our study with children aged between 6-16 years and presented with moderate-severe acute asthma attack, there was no significant difference between two groups in terms of retraction, auscultation, PEFR level, and AAS. However, improvement rates of all parameters evaluated were higher in the group 2.

Leukotriene receptor antagonists are the drugs used in asthma treatment in the last 20 years. There are numerous studies about the favorable effects of these drugs in the treatment of chronic asthma, whilst there are few studies about their role in the treatment of acute asthma attacks.

There are studies stating that the use of montelukast in addition to the standard management improves significantly FEV-1 and PEFR and reduces the rate of hospitalization in adult patients with acute asthma (11,2). However, there are limited

number of studies about the benefits of montelukast use in addition to the standard treatment in the childhood period.

In a single-blind, randomized, placebo-controlled study, Çilli et al. (13) investigated whether montelukast, oral leukotriene receptor antagonist, provided further benefit in the patients with acute asthma, who had received first-line treatment involving inhaled terbutaline and corticosteroid. That study is the first trial to ascertain the efficacy of montelukast in acute exacerbation of asthma. At the time of initial admission, PEFR and FEV-1 measurements were done. Then, the patients were randomly divided into 3 groups; the first group was given montelukast 10 mg tablet orally plus 1 mg/kg steroid intravenously, the second group was given steroid alone and the third group was given placebo treatment. Immediately after that treatment, the patients were given aerosol terbutaline sulfate 0.5 mg dry powder inhaler (Bricanyl turbohaler 0.5 mg) 3 times with 20-minute intervals. The patients were monitored throughout 24 hours for PEFR changes, Borg dyspnea score and additional therapeutic needs. In our study, the patients were given inhaled salbutamol, inhaled ipratropium bromide and oral methyl prednisolone as initial treatment, and their respiratory parameters, PEFR value, AAS score were evaluated 8 times throughout 4 hours.

Çilli et al (13). reported that PEFR values of the patients receiving montelukast plus corticosteroid and those receiving steroid alone were significantly higher than that of the patients given placebo. PEFR values of the patients given montelukast plus corticosteroid were found to be higher than that of the patients given steroid alone, however, the difference between these two groups was not significant. The maximum percentage of the increase in PEFR values throughout 24 hours was 42% in the group of patients given montelukast plus corticosteroid, 39.9% in the group given steroid alone and 10.3% in the group receiving placebo. Similar to these data, in our study, there was no statistically significant difference between the group of patients given montelukast (group 2) and the placebo group (group 1) in terms of PEFR values, however, the average PEFR levels of group 2 patients were found to be higher than that of the group 1 patients. At the end of 4 hours, the rate of increase in PEFR was 67.64% in the group 2, but it was 46.48% in the group 1. Even though the difference was not statistically significant, it was thought that the use of montelukast in addition to acute treatment could contribute to improvement of PEFR. Çilli et al (13). found that Borg dyspnea scores of the groups given treatment were significantly lower than that of placebo group; however, the authors did not find any difference between the treatment groups. In our study, there was no significant difference between the groups in terms of dyspnea score, but the percentage of decline in the scores was higher in the group 2. In the study performed by Çilli et al (13), the group of the patients given steroid plus montelukast required adjunctive -acting inhaler B-agonist less often in comparison with the patients given steroids alone, but there was no difference between three groups in terms of this matter. In our study, after 4-hour monitoring following the treatment, we did not find any patient, who required additional treatment and discharged all patients prescribing their medicines. In contrast to the study performed by Çilli et al (13). We evaluated retraction, saturation and respiratory rate of the patients during the study period. The rates of improvement in these parameters were also higher in the group II, however, there was no significant difference.

Todi et al. (14) researched the benefits of oral montelukast used in addition to the standard treatment in children aged between 5-12 years with moderate-severe acute asthma attack (modified pulmonary index score- MPIS $\geq$9). In that study, MPIS and FEV-1 values of the patients were recorded at the time of hospital admission and then hourly throughout four hours. The criterion for efficacy of the drugs was defined as a MPIS point below nine. At the end of four-hour monitoring, 63.2% of the patients given montelukast and 55% of the patients not receiving montelukast had MPIS below nine. There was difference between the results, however, it was not found to be significant statistically. There was no difference between the groups in terms of hospitalization rates and side effects. In our study, the ages of the study patients ranged from 6 to 16 years. We did not identify any

patient who had the illness as severe as requiring hospitalization and we did not find any difference in terms of adverse effects pattern. However, we evaluated more parameters and monitored the patients more frequently.

In another placebo-controlled study with children aged between 6-14 years with acute asthma attack, Morris et al (15). researched the effects of 5.25 mg montelukast given intravenously in addition to standard regimen on the average FEV-1 value at 60 minutes, MPIS and presenting symptoms. The drugs were tolerated well in both groups. However, the authors did not find any difference between the groups in terms of FEV-1 values, alleviation of presenting symptoms, and average hospital stay (15). In that study, in contrast to our trial, montelukast was administered intravenously. However, the children were evaluated only once and they were not monitored after 60 minutes. In our study, montelukast was given via oral route , the patients were monitored throughout 240 minutes and were evaluated 8 times during this period. That Morris et al (15). evaluated the treatment response using FEV-1 evaluation makes the study significant.

Another placebo-controlled trial studied the effect of the addition of oral montelukast to the standard regimen on FEV-1 during three-hour monitoring of children aged 6-14 years with moderate acute asthma attack. At the end of three hours, the researchers found the average increases in FEV-1 in both groups to be similar (16).

In a placebo-controlled study from our country, Harmancı et al. (17) studied the effects of 4 mg montelukast used in addition to short-acting beta-2 agonist on the pulmonary index score (PIS), respiratory rate and heart rate after four hour monitoring among children aged between 2-5 years with mild-moderate asthma attack. The authors found that at 90 minutes, PIS and respiratory rate of montelukast group were significantly lower than that of placebo group. That difference was also observed at 120, 180 and 240 minutes. At the end of one-hour treatment, 20.8% of the patients in the montelukast group and 38.5% of the patients in the placebo group required oral steroid. The difference between the groups was not found to be significant. There was no difference between the groups in terms of hospitalization rates. The authors defined that montelukast used in addition to short-acting beta-2 agonist provided additional clinical benefits in pre-school children presented with mild and moderate acute asthma attack. That study differs from our trial because of younger patient series, asthma attack severity (inclusion of the patients with mild and moderate asthma attacks), and the differences in the parameters evaluated during 4-hour monitoring and in the treatment regimen. Harmancı et al. used oral montelukast, as we did, since intravenous montelukast is not available in our country.

The main restriction of our study is the small patient series, it is related to our large number of exclusion criteria that we established to make the specificity higher. Another limitation of our study is unavailability of intravenous form of montelukast in our country, so that its oral form is used in the study.

In conclusion, the studies about the effects of montelukast on acute asthma attack in pediatric patients differ in terms of parameters evaluated, patient's age, severity of asthma attack. The limited number of studies about this matter and conflicting results make difficult to commentate. However, montelukast is used safely in chronic asthma management and with the studies about its use in acute asthma attack in children, it has been demonstrated that it is a well-tolerated drug. It was found that the patients given additional montelukast showed better PEFR improvement and clinical recovery, although some of these studies and our trial demonstrated no significant difference in comparison with control groups. Therefore, we think that the use of montelukast can offer additional benefit to improve PEFR and asthma attack scores in children presented with acute asthma attack.

KAYNAKLAR

1. E.R. McFadden,Jr. Acute Severe Asthma. Am J Respir Crit Care Med 2003, 168: 740-759
2. Reiss TF, Sorkness CA, Stricker W. Effects of montelukast, a potent cysteinyl leıkotriene receptor antogonist, on bronchodilation in asthmatic subjects treated with and without inhaled corticosteroids. Thorax 1997; 52: 45-48.
3. National Heart, Lung and Blood Institute, World Health Organisation. Global Initiative for Asthma. management and prevention 2006.
4. Williams SG, Schmidt DK, Redd SC, Storms W. Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. MMWR Recomm Rep. 2003 Mar 28;52(RR-6):1-8.
5. Pişgin Volkan B. Hafif persistan ve orta persistan astımlı çocuklarda montelukast ile zafirlukastın etkinliğinin karşılaştırılması. İstanbul 2008 Uzmanlık tezi.
6. Salvi SS, Krishna MT, Sampson AP. The anti inflammotory effects of leukotriene modifiying drugs and their use in asthma. Chest 2001; 119:1533-1546.
7. Knoor B, Franchi L, Bisgaard M, et al. Montelukast, a leukotriene receptor antagonist, for the treatment persistent asthma in children aged 2 to 5 years. Pediatrics 2001; 180: 48.
8. Kay AB, Bousquet J, Holt PG, Kaplan AP. Allergy and Allergic Diseases. Currie GP, Lipworth BJ. Antileukotrien agents. 2nd edition, Volume-1, Wiley-Blackwell publishing, 2008, 694-714
9. Castro Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A Clinical index to define risk of asthma in young children with recurrent wheezing .Am J Respir Crit Care Med 2000; 162: 1403-1406
10. Skoner D. Montelukast in 2- to 5- Year- Old Children With Asthma. Pediatric Pulmonology (Suppl) 2001; 21: 46-48
11. Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. Thorax 2010; 18. [Epub ahead of print].
12. Camargo CA Jr, Gurner DM, Smithline HA, Chapela R, Fabbri LM, Green SA, Malice MP, Legrand C, Dass SB, Knorr BA, Reiss TF. A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma. J Allergy Clin Immunol 2010; 125(2): 374-380.
13. Çilli A, Kara A, Ozdemir T, Oğüş C, Gülkesen KH. Effects of oral montelukast on airway function in acute asthma. Respir Med 2003; 97(5): 533-536.
14. Todi VK, Lodha R, Kabra SK. Effect of addition of single dose of oral montelukast to standard treatment in acute moderate to severe asthma in children between 5 and 15 years of age: a randomised, double-blind, placebo controlled trial. Arch Dis Child 2010; 95(7): 540-543. Epub 2010 Jun 3.
15. Morris CR, Becker AB, Piñieiro A, Massaad R, Green SA, Smugar SS, Gurner DM. A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma. Ann Allergy Asthma Immunol 2010; 104(2): 161-171.
16. Nelson KA, Smith SR, Trinkaus K, Jaffe DM. Pilot study of oral montelukast added to standard therapy for acute asthma exacerbations in children aged 6 to 14 years. Pediatr Emerg Care 2008; 24(1): 21
17. Harmanci K, Bakirtas A, Turktas I, Degim T. Oral montelukast treatment of preschool-aged children with acute asthma. Ann Allergy Asthma Immunol. 2006; 96(5): 731-735.