http:// ijp.mums.ac.ir
Original Article (Pages: 4257-4262)

The Efficacy of Montelukast in Adjunct with Amoxicillin in Treatment of Acute Otitis Media (AOM) in Children

Mohammad-Bagher Rahmati[1], Salehe Sabouri[2], *Fatemeh Sabouri[1]

[1]Clinical Research Development Center of Children Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
[2]Herbal & Traditional Medicines Research Center, Kerman University of Medical Sciences, Kerman, Iran.

Abstract

Background
Acute otitis media (AOM) is very common in children. In spite of spontaneously relief, some cases suffer from the recurrence and other complications occurring after AOM. Animal studies have proved that persistence of leukotrienes in the middle ear may play a role in the development of AOM. Based on this statement, treatment with leukotriene modifiers may be effective in the treatment of OM. The aim of this study was to examine the effect of adjunction of montelukast to antibacterial agents in treatment of AOM.

Materials and Methods
One hundred patients aged 2-6 years were randomly divided into two groups. One of the groups (53%) were treated with "amoxicillin alone", 80-90 mg/kg amoxicillin for 10 days, and the other group (47%), received "amoxicillin and montelukast" 5 mg per day orally for 10 days. Patients were evaluated for resolution and complications of AOM at 2 post enrollment visits (days 2-4 and 10-14).

Results
The patient followed-up for one month and results showed that, treatment with montelukast had beneficial effects on resolution of AOM. In monotherapy (amoxicillin alone) group, 66% of patients and in the montelukast (amoxicillin and montelukast) group, 85.1% were treated.

Conclusion
In this study, the montelukast receiving group showed a better response to treatment. Based on this and previous studies, it is recommended to consider the role of inflammatory mediators in AOM. Prescribing montelukast and other leukotriene receptor antagonists may have benefits for the patients.

Keywords: AOM, Amoxicillin, Children, Leukotriene modifier, Montelukast.

*Please cite this article as: Rahmati MB, S Sabouri S, Sabouri F. The Efficacy of Montelukast in Adjunct with Amoxicillin in Treatment of Acute Otitis Media in Children. Int J Pediatr 2017; 5(1): 4257-62. DOI: **10.22038/ijp.2016.7803**

Corresponding Author:

Fatemeh Sabouri, Clinical Research Development Center of Children Hospital, Daroopakhsh Avenue, north Golshahr, Bandar Abbas, Iran, 7915873665. Fax: +987633667201

Email: saboori_fatemeh@yahoo.com

Received date Nov. 12, 2016; Accepted date: Dec. 22, 2016

1- INTRODUCTION

Acute otitis media (AOM) is one of the most common diseases of childhood and occurs at least once in about 70% of children under 2 years old (1, 2). Almost 80% of cases of AOM relieve spontaneously, however, antibiotics are commonly used in its treatment. Because of the recurrence and some complications occurring after AOM such as otitis media with effusion (OME), it is still a considerable disease and researches are performing to find a better treatment strategy for that (3, 4). The main cause of otitis media (OM) is bacteria. The most common bacterial causes of AOM are *Streptococcus pneumonia* and *Haemophilus influenzae* (5, 6).

However, the inflammatory responses have been proven to cause the recurrence or persistence of AOM (3). It is believed that the bacterial endotoxin is the initiator of inflammation in middle ear. It induces secretion of inflammatory mediators and stimulates immune cells (5). Leukotrienes are of the most important pro-inflammatory mediators with activities like vasoconstriction and increased vascular permeability. These mediators are secreted by neutrophils, mast cells, basophils and eosinophils (5-7).

Tada et al. showed that injection of leukotrienes C4 (LTC4), into rat middle ear can induce OME (8). Thus, adding leukotriene receptor inhibitors to antibiotic therapy regimen may have positive impacts on the prevention from development of AOM to OME (7).

Montelukast sodium is a selective antagonist of LTD4 receptor (9, 10). It is approved for treatment of chronic asthma and is safe and tolerable in children and adults (11-13). Animal studies showed effectiveness of leukotriene receptor antagonists (montelukast and pranlukast) in treatment of OM (6, 8, 14). However, clinical studies reported controversial results (7, 15, 16). Therefore, the aim of this study was to examine the therapeutic effect of montelukast in AOM and its prophylactic effect from progression of AOM to further complications.

2- MATERIALS AND METHODS

2-1. Study design

This randomized single-blind control trial was conducted at Bandar Abbas children hospital pediatric ambulatory clinic, South West of Iran from December 2015 to February 2016. All the procedures of this study were carried out according to the declaration of Helsinki. Additionally, the study was approved by ethics committee of Hormozgan University of Medical Sciences by the code of HUMS.REC.1394.62. It was also registered in Iranian Registry of Clinical Trials (registration number: IRCT2016040627236N2).

2-2. Patients

A total of 104 children aged 2-6 years were included in this study. The inclusion criteria were:

- Age 2 to 6 years and
- Diagnosis of acute otitis media.

The exclusion criteria were:

- 1. Receiving prophylactic steroids or montelukast, 2. Patients with chronic lung or heart disease or immune deficiency (primary, secondary),
- 3. Long medication for any reason,
- 4. Sensitivity to montelukast,
- 5. Lack of parental cooperation, and
- 6. Need to change antibiotics during the study.

2-3. Diagnosis and intervention

The otalgia, fever, irritability, lethargy, otorrhea, anorexia, and vomiting were considered as the general signs of the disease and the diagnosis of eardrum

bulging by pneumatic otoscopy was regarded as the specific symptom (4). A questionnaire including gender, age, a history of allergy to medicines, and drug of use at the time of study was filled by parents. After parents provided written consent, patients were randomly divided into two groups: the first group received only 80-90 mg/kg amoxicillin (17) for 10 days and the second group received 5 mg once daily oral montelukast in addition to amoxicillin for 10 days. Patients were evaluated for resolution and complications of AOM at 2 post enrollment visits, the first one was between days 2 to 4 and the second was between days 10 to 14.

The evaluation was based on parental reports of the relief of symptoms (otalgia, fever, irritability, etc.) and clinical findings at post enrollment visits. The patients were examined before and after treatment by the same physician. The other physician prescribed medications to the patients and categorized them into 2. In this way, the examiner was blinded about the intervention. The patients were also followed for one month.

2-4. Statistical analysis

Data were analyzed in SPSS version 16.0 software. The student's t-test was used to analyze the continuous variables. The Pearson Chi-square was used to analyze the differences between measured factors. The P-values <0.05 were considered as statistically significant.

3- RESULTS

The prescribed antibiotic of two out of 104 patients (from treatment group receiving amoxicillin and montelukast) was changed, so they were excluded from the study. This was because of the incidence of amoxicillin side effects (diarrhea and rash). Two other patients (from treatment group receiving amoxicillin and montelukast), also were excluded from the study since they did not continue the treatment. The mean age of patients was 3.97± 2.16 years old. The demographic characteristics and clinical findings of the two groups are presented in **Table.1**. Twenty nine (54.7%) of girls were in group amoxicillin and 18 (38.3%) in group amoxicillin+ montelukast. Twenty four (45.3%) of boys were placed in group amoxicillin and 29 (61.7%) in group amoxicillin+ montelukast. There was not a significant difference between these distributions although it was near significance (P=0.075).

The difference between distribution of the age groups (age 2-4 and 4-6 years) in two-groups, also was not significant (P= 0.119). The presented data of **Table.1** shows that the difference between response to the treatment in two groups is significant, but it is not significant for the incidence of complications (P=0.075). **Figure.1** shows the number of treated subjects, occurrence of complications acute mastoiditis otitis media with effusion (OME), perforation and recurrence in two interventional groups.

Table-1: Demographic characteristics and clinical finding of all subjects and the two treatment groups

Variables		Treatment group		P-value
		Amoxicillin	Amoxicillin + montelukast	
Gender	Female	29 (54.7%)	18 (38.3%)	0.075
	Male	24 (45.3%)	29 (61.7%)	
Age group	2-4 years	31 (59.6%)	21 (40.4%)	0.119
	4-6 years	22 (45.8%)	26 (54.2%)	
Affected ear	Right	22 (46.8%)	25 (53.2%)	0.444
	Left	23 (43.4%)	30 (56.6%)	

Treatment results	Treated	Yes	35 (66.0%)	40 (85.1%)	0.007
		No	18 (34%)	7 (14.9%)	
	Complication	Yes	15 (28.3%)	5 (10.6%)	0.075
		No	38 (71.7%)	42 (89.4%)	
	Perforation	Yes	3 (5.7%)	2 (4.3%)	0.067
		No	50 (94.3%)	45 (95.7)	
	Recurrence	Yes	1 (1.9%)	0	0.530
		No	52 (98.1%)	47 (100%)	
Patients total No.			53	47	

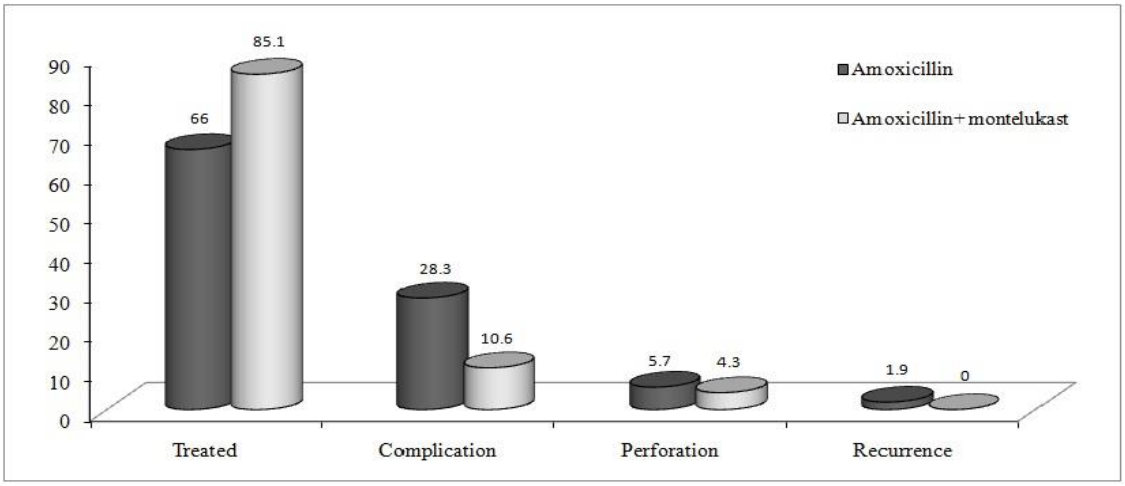

Fig.1: Comparison between treated subjects, occurrence of complication, perforation, and recurrence between the two interventional groups (%).

4- DISCUSSION

Several reports affirmed the persistence of leukotrienes in the middle ear effusions. This leads to the estimation that these inflammatory mediators play an important role in the pathology of OM and progression of AOM to OME (6, 18, 19). Montelukast, a selective leukotriene receptor inhibitor, can prevent binding of LTD4 to its receptor and antagonize its effects such as vascular permeability, mucus formation and others (5). Our findings demonstrated the efficacy of montelukast in treatment of AOM (85% in montelukast group versus 66% in control group), but not for the prevention from incidence of complications.

Combs investigated the effect of montelukast on the duration of effusion in 29 children with acute otitis media for 1 month and reported the efficacy of this treatment 58% versus 16% in 31 patients of placebo group (7). In 2010, Schoem et al. reported the inefficacy of montelukast in treatment of children with OME and discontinued the study (15). However, Ertugay et al. in 2013 described the benefits of treatment of OME with montelukast and levocetirizine (16). It is noteworthy to point out the sample size in our study was larger than these studies.

There are also animal experiments investigating the effect of leukotriene modifiers in treatment of OM (AOM and OME). Ucar et al. reported that montelukast was as effective as penicillin in relieving AOM symptoms in rats infected with transtympanically injected Pneumococcus suspension (6). Aynali et al. treated rats with OME with methylprednisolone, montelukast, and indomethacin. The results showed that methylprednisolone was the most and indomethacin was the least effective drug. Montelukast was more effective than indomethacin and the difference was

significant (14). In Tada et al. pranlukast, another leukotriene modifier, was used in treatment of experimental OME in rats. The treatment was reported as effective (8). Most of the experiments reporting the efficacy of montelukast in treatment of AOM or OME were performed in animals. The clinical studies were controversial, so in this study, montelukast was used for treatment of AOM in human subjects with a larger sample size. Our results confirm Combs (7) and Ertugay et al. (16), whom reported the efficacy of montelukast in treatment of OM. However, using montelukast in our study did not show a significant preference in occurrence of complications.

4-1. Limitations of the study

Prescribing amoxicillin may have confounded the effect of montelukast. Also having no placebo was another limitation of this study. However, we blinded the examiner about the prescribed medicine/ medicines.

5- CONCLUSION

As the montelukast receiving group showed a better response to treatment based on the results of this and previous studies, and also considering the safety of montelukast (11-13), it is recommended to consider the role of inflammatory mediators especially leukotrienes in AOM and prescribe montelukast as an adjunct to antibiotics for the treatment of AOM. It is also suggested to use leukotriene receptor inhibitors in a large clinical trial to confirm the results of these performed trials.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGEMENTS

We are thankful to our counselors in Clinical Research Development Center of Children Hospital. This work was supported by Hormozgan University of Medical Sciences [grant numbers 183]. We would also like to thank children and their parents who participated in this study.

8- REFERENCES

1.Worrall G. Acute otitis media. Can Fam Physician 2007;53(12):2147-8. PubMed PMID: 18077757. Pubmed Central PMCID: 2231558.

2. Stevanovic T, Komazec Z, Lemajic-Komazec S, Jovic R. Acute otitis media: to follow-up or treat? Int J Pediatr Otorhinolaryngol 2010;74(8):930-3. PubMed PMID: 20599127.

3. Aladag I, Guven M, Eyibilen A, Sahin S, Koseoglu D. Efficacy of vitamin A in experimentally induced acute otitis media. Int J Pediatr Otorhinolaryngol 2007;71(4):623-8. PubMed PMID: 17303254.

4. Qureishi A, Lee Y, Belfield K, Birchall JP, Daniel M. Update on otitis media - prevention and treatment. Infect Drug Resist 2014;7:15-24. PubMed PMID: 24453496. Pubmed Central PMCID: 3894142.

5. Juhn SK, Jung MK, Hoffman MD, Drew BR, Preciado DA, Sausen NJ, et al. The role of inflammatory mediators in the pathogenesis of otitis media and sequelae. Clin Exp Otorhinolaryngol 2008;1(3):117-38. PubMed PMID: 19434244. Pubmed Central PMCID: 2671742.

6. Ucar S, Huseynov T, Coban M, Sarioglu S, Serbetcioglu B, Yalcin AD. Montelukast is as effective as penicillin in treatment of acute otitis media: an experimental rat study. Med Sci Monit Basic Res 2013;19:246-52. PubMed PMID: 24048018. Pubmed Central PMCID: 3808231.

7. Combs JT. The effect of montelukast sodium on the duration of effusion of otitis media. Clin Pediatr (Phila). 2004;43(6):529-33. PubMed PMID: 15248005.

8. Tada N, Furukawa M, Ogura M, Arai S, Adachi Y, Ikehara S, et al. Experimental otitis media with effusion induced by leukotriene D4. Auris Nasus Larynx 2002;29(2):127-32. PubMed PMID: 11893446.

9. Jones TR, Labelle M, Belley M, Champion E, Charette L, Evans J, et al. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D4 receptor antagonist. Can J Physiol

Pharmacol 1995;73(2):191-201. PubMed PMID: 7621356.

10. De Lepeleire I, Reiss TF, Rochette F, Botto A, Zhang J, Kundu S, et al. Montelukast causes prolonged, potent leukotriene D4-receptor antagonism in the airways of patients with asthma. Clin Pharmacol Ther. 1997;61(1):83-92. PubMed PMID: 9024176.

11. Bisgaard H, Skoner D, Boza ML, Tozzi CA, Newcomb K, Reiss TF, et al. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. Pediatr Pulmonol. 2009;44(6):568-79. PubMed PMID: 19449366.

12. Storms W, Michele TM, Knorr B, Noonan G, Shapiro G, Zhang J, et al. Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged > or = 6 years. Clin Exp Allergy 2001;31(1):77-87. PubMed PMID: 11167954.

13. Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. N Engl J Med 1998;339(3):147-52. PubMed PMID: 9664090.

14. Aynali G, Yariktas M, Yasan H, Karahan N, Baspinar S, Tuz M, et al. The effects of methylprednisolone, montelukast and indomethacine in experimental otitis media with effusion. Int J Pediatr Otorhinolaryngol 2011;75:15-9.

15. Schoem SR, Willard A, Combs JT. A prospective, randomized, placebo-controlled, double-blind study of montelukast's effect on persistent middle ear effusion. Ear Nose Throat J 2010;89(9):434-7. PubMed PMID: 20859868.

16. Ertugay CK, Cingi C, Yaz A, San T, Ulusoy S, Erdogmus N, et al. Effect of combination of montelukast and levocetirizine on otitis media with effusion: a prospective, placebo-controlled trial. Acta Otolaryngol. 2013;133(12):1266-72. PubMed PMID: 23972320.

17. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964-99. PubMed PMID: 23439909.

18. McCormick DP, Saeed K, Uchida T, Baldwin CD, Deskin R, Lett-Brown MA, et al. Middle ear fluid histamine and leukotriene B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. Int J Pediatr Otorhinolaryngol 2003;67(3):221-30. PubMed PMID: 12633920.

19. Brodsky L, Faden H, Bernstein J, Stanievich J, DeCastro G, Volovitz B, et al. Arachidonic acid metabolites in middle ear effusions of children. Ann Otol Rhinol Laryngol 1991;100(7):589-92. PubMed PMID: 1648326.