ORIGINAL ARTICLE

Comparison of Montelukast Versus Placebo For Management of Acute Bronchiolitis in Children.

RAISA TASNEEM[1], SADIA SHABIR, MUHAMMAD ALI[3], SHAFAQ AZIZ[4], BUSHRA AHMAD[5], NUDRAT RASHID[6]
[1]*Medical Officer*
[2]*Assistant Professor KEMU/ Mayo Hospital, Lahore*
[3]*Visiting Faculty KEMU, Lahore. Associate Professor CMC/HMTH*
[4]*Senior Registrar Mayo Hospital Lahore*
[5]*Senior Registrar Mayo Hospital Lahore*
[6]*Assistant Professor Gynae Unit 3 SIMS / Services Hospital*
Correspondence to: Dr. Rasa Tasneem, Email: ras_genez@hotmail.com, Contact: 03324808603

ABSTRACT

Bronchiolitis is result of inflammatory response of the body in the respiratory tract leading to the obstruction of the small airways (bronchioles and alveoli), in young children of less than two years age. Fever, nasal discharge, tachypnea, expiratory wheeze and/or fine inspiratory crackles are clinical features of this disease[1].

Objective: To compare the mean clinical severity score and hospital stay after montelukast versus placebo as an adjunct for management of acute bronchiolitis in children.

Duration of Study: February 23, 2017 to August 23, 2017

Study Design: Randomized controlled trial

Methodology: All 100 patients fulfilling the operational definition of acute bronchiolitis admitted in pediatric emergency were evaluated by the primary investigator. Children were given Montelukast 5mg chewable form as an adjunct to standard treatment in interventional group and children in non-interventional group were given placebo as an adjunct to standard treatment. Clinical severity score was assessed and all children were admitted in pediatric ward and were followed-up there for 3 days. After 3 days of treatment, clinical severity score was again measured. Data were analyzed using SPSS v23.0. Post-stratification, independent sample t-test was applied. p-value ≤0.05 was considered significant.

Results: Of total 100 patients 50 patients were given Montelukast and 50 patients were given placebo. The Mean clinical severity score of patients in group A was 0.07±0.03 and in group B was 0.48±0.32 with p-value of 0.000 which is statistically significant. The mean hospital stay of patients in group A was 36.4±3.8 hours and in group B was 54.3±3.7 hours with p-value of 0.000 which is statistically significant.

Conclusion: Montelukast can be recommended to physicians treating bronchiolitis patients. It can significantly reduce the signs and symptoms of the disease, thus decreasing the disease severity along with the stay in the hospital. Study should be done on a larger population in various cities of our country to see the effect of montelukast on various populations.

Keywords: Bronchiolitis, Montelukast, Clinical Severity Score, Medically fit for Discharge.

INTRODUCTION

Bronchiolitis is result of inflammatory response of the body in the respiratory tract leading to the obstruction of the small airways (bronchioles and alveoli), in young children of less than two years age. Fever, nasal discharge, tachypnea, expiratory wheeze and/or fine inspiratory crackles are clinical features of this disease[1].

Disease severity depends upon some risk factors which decide admission of the patient and overall prognosis and outcome of disease. Most common risk factor is patient age. Other factors include prematurity, congenital heart disease, history of smoker in the family, history of NICU admission, day-care babies and socio economic deprivation[2].

According to SIGN91 guideline acute sever bronchiolitis is labeled when patient has poor feeding, lethargy, history of apnea, respiratory rate >70/min, presence of nasal flaring and/or grunting, severe chest wall recession, cyanosis. According to NICE Guideline, persistent oxygen saturation of less than 92% is another important criteria[3].

Various studies have shown that there is significant morbidity of this disease but have a low mortality rate. Around 1/3rd of young children of age < 2 years are affected. Rate of hospitalization varies within populations and developed countries from 3% to 7%[4].

Different treatments modalities have been used for treatment of acute sever bronchiolitis. Inhaled medication through metered- dose inhaler with mask and spacer is used. Ipratropium bromide is effective as adjunct therapy, inhaled/oral steroids has been used particularly in those who have sever wheezing with history of atopic. Otherwise, cool humidified oxygen with prop-up position and frequent suction of nasal and oral secretion has proved beneficial. Moreover, Bronchodilators, corticosteroids, Ribavirin, nebulization with hypertonic saline have also been used. Heliox delivered by tight fitting mask or by continuous positive airway pressure has been of some benefit in moderate to severe affected patients with bronchiolitis[5].

Montelukast, a leukotriene receptor antagonist, is commonly added to the medical treatment of atopic patients. It is a competitive inhibitor of cysteinyl leukotriene type-1 receptor especially in the respiratory epithelium. This effect can reduce inflammatory makers associated changes in the surrounding tissue. Some studies have hypothesized that it may lead to significant reduction in the bronchial inflammatory response of the body by reducing

mucosal edema, thus preventing broncho-constriction in infants with bronchiolitis[6].

A study was conducted in Lahore on sixty children with acute bronchiolitis showed that mean clinical severity score was 0.0667±0.25371 with montelukast and 0.6833±1.02118 with placebo (p=0.002) and the mean hospital stay was 37.60±15.73 hours with montelukast and 59.2±19.58 hours with placebo (p=0.002)[7].

As bronchiolitis is prevalent in our region with significant morbidity and mortality, early diagnosis and intervention taken in the management can significantly reduce the disease severity. The aim of this study is to determine the efficacy of montelukast in terms of mean clinical severity score and hospital stay versus placebo, used as an adjunct in the management of acute bronchiolitis in infants and children.

MATERIAL AND METHODS

In this Randomized Controlled Trial, conducted in Pediatrics ward and emergency, in Mayo Hospital, Lahore (between February 23, 2017 to August 23, 2017), 100 cases were included using sampling Technique of non-probability consecutive sampling.

Total hundred (100) cases (50 patients for one group and 50 for other group) was calculated using 95% confidence level, 80% power of test and mean clinical Severity Score i.e. 0.0667 ± 0.25371 with montelukast and 0.6833 ± 1.02118 with placebo for management of acute bronchiolitis in children[8].

All infants and children of age 03 to 24 months of either gender meeting the operational definition of acute bronchiolitis diagnosed during last 72 hours (as per operational definition) were included for this randomized controlled trial.

Exclusion criteria:

1. Previous wheezing episode, confirmed asthma, bronchiolitis (on medical record)
2. Recent bronchodilator or Immunosuppressive drug use (on medical record)
3. Croup or pneumonia diagnosis (on medical record)

Patients were included after proper informed consent taken from the parents. Variables including age, sex, weight were noted. Children were given Montelukast 5mg chewable form as an adjunct to standard treatment in interventional group and children in non-interventional group were given placebo as an adjunct to standard treatment. Clinical severity score was assessed and all children were admitted in pediatric ward and were followed-up there for 3 days. After 3 days of treatment, clinical severity score was again measured (as per operational definition). Children were discharged when medically fit for discharge and length of hospital stay was noted. All this information was recorded on proforma (attached).

The collected data were analyzed statistically by using SPSS v23.0. Quantitative variables like age, weight, clinical severity score (at baseline and after treatment) and hospital stay, were analyzed and there Mean ± S.D was calculated. Qualitative variables like gender were presented in form of frequency and percentage. Both groups were compared for mean clinical severity score and hospital stay by using independent sample t-test. P-value≤0.05 was considered as significant. Data were stratified for age, gender and weight. Post-stratification, independent sample t-test was applied with p-value≤0.05 taken as significant.

RESULTS

Total 100 patients were enrolled in this study. Patients were divided in two group's i.e. Group-A (Montelukast) and Group-B (Placebo). The mean age of patients in group A was 13.1±6.0 months and in group B was 11.4±6.5 months. Mean clinical severity score of patients in group A was 0.07±0.03 and in group B was 0.48±0.32.

The mean hospital stay of patients in group A was 36.4±3.8 hours and in group B was 54.3±3.7 hours. In group-A, there were 35(70.0%) were males and 15(30.0%) were females. In group-B, 26(52.0%) were males and 24(48.0%) were females. In group-A, there were 32(64.0%) of weight 5-9 kg and 18(36.0%) of weight >9 kg. In group-B, 22(44.0%) were of weight 5-9 kg and 28(56.0%) of weight >9 kg.

The Mean clinical severity score of patients in group A was 0.07±0.03 and in group B was 0.48±0.32 with p-value of 0.000 which is statistically significant. The mean hospital stay of patients in group A was 36.4±3.8 hours and in group B was 54.3±3.7 hours with p-value of 0.000 which is statistically significant.

Table-1: Showing comparison of various variables between the two groups

Gender	Groups		Total
	Montelukast	Placebo	
Male	35	26	61
	57.4%	42.6%	100.0%
Female	15	24	39
	38.5%	61.5%	100.0%
Total	50	50	100
	50.0%	50.0%	100.0%

Age groups	Groups		Total
	Montelukast	Placebo	
≤12 months	24	32	56
	42.9%	57.1%	100.0%
>12 months	26	18	44
	59.1%	40.9%	100.0%
Total	50	50	100
	50.0%	50.0%	100.0%

Weight	Groups		Total
	Montelukast	Placebo	
5-9 kg	32	22	54
	59.3%	40.7%	100.0%
>9 kg	18	28	46
	39.1%	60.9%	100.0%
Total	50	50	100
	50.0%	50.0%	100.0%

Table-2: showing stratification with respect to gender, age and weight for comparison of clinical severity score between groups

Gender	Groups	N	Mean	Std. Deviation	p-value
Male	Montelukast	35	0.07	0.03	0.000
	Placebo	26	0.47	0.31	
Female	Montelukast	15	0.07	0.03	0.000
	Placebo	24	0.49	0.33	
Age	Groups	N	Mean	Std. Deviation	p-value
≤12 Months	Montelukast	24	0.064	0.029	0.000
	Placebo	32	0.520	0.288	
≥12 Months	Montelukast	26	0.084	0.035	0.000
	Placebo	18	0.413	0.371	
Weight	Groups	N	Mean	Std. Deviation	p-value
5-9 kg	Montelukast	24	.064	.029	0.000
	Placebo	32	.520	.288	
>9 kg	Montelukast	26	.084	.035	0.000
	Placebo	18	.413	.371	

Table-3: Showing stratification with respect to gender, age and weight for comparison of hospital stay between groups

Gender	Groups	N	Mean	Std. Deviation	p-value
Male	Montelukast	35	36.34	3.82	0.000
	Placebo	26	56.31	2.90	
Female	Montelukast	15	36.73	3.88	0.000
	Placebo	24	52.29	3.42	
Age	Groups	n	Mean	Std. Deviation	p-value
≤12 Months	Montelukast	24	35.92	4.16	0.000
	Placebo	32	54.06	3.93	
≥12 Months	Montelukast	26	36.96	3.45	0.000
	Placebo	18	54.94	3.35	
Weight	Groups	n	Mean	Std. Deviation	p-value
5-9 kg	Montelukast	32	36.13	3.82	0.000
	Placebo	22	53.41	4.04	
>9 kg	Montelukast	18	37.06	3.81	0.000
	Placebo	28	55.14	3.33	

DISCUSSION

Despite the prevalence of bronchiolitis with significant severity in our region, along with seasonal variations, it still can be regarding as the commonest lower respiratory tract infection of infancy. With a lot of data and research done globally to plan a proper treatment plan, signs and symptoms of bronchiolitis can be controlled but tiemly decisions matters. Still there is no consensus on one management plan for this disease. Mild inhaled corticosteroids with bronchodilators can help in restoring the function of the lungs. Montelukast, if given early in the disease period, can modify its course; it can even reduce the chances of development of severe signs and symptoms, thus reducing hospital stay, chances of development of significant morbidity and preventing mortality.

Studies have shown that infants of bronchiolitis, if not treated properly, are prone to develop wheeze later in life. Clinical trials have shown that infants with hyper-active airways have history of recurrent attacks of bronchiolitis in infancy. Early use of Montelukast in infants with recurrent bronchiolitis can modify the risk of development of acute asthmatic attacks[7].

Still many studies done to see the role of montelukast in the prevention and treatment of bronchiolitis and wheezing shows in-significant results. These studies could't see any significant difference in the hospital stay and disease severity. Some studies compared its combination treatment (montelukast along with corticosteroids), still the results of few studies were in-consistent. Outcome of patient in which montelukast was used along with corticosteroids was not significantly different from that with corticosteroid use alone[8,9].

Studies supporting the role of montelukast in bronchiolitis and wheezing are also available. Many authors found it significantly useful as a modifier of episodic attacks of asthma and acute viral respiratory infections.[i] Similar results were seen in our study, in which montelukast use clearly reduced the use of oral corticosteroids in the treatment of bronchiolitis along with significant reduction in hospital stay.

As sufficient data is lacking in regard to the along use of montelukast in these infections in infants and children, currently pediatricians in our country are treating infants with bronchiolitis conventionally with salbutamol nebulization. Literature is still lacking regarding the use of montelukast alone as a therapeutic agent to prevent and treat bronchiolitis.

Nebulization was done at a regular interval; using a specific dose in both groups without labels thus bias was removed all the way till the intervention. Among all the patients included in the study, youngest was of age 3 months (mean age 13.1 months). After data analysis, it was seen that no adverse effects were seen in these children. Studies have shown that the safety of this drug is established even for the age of one month old infant[11].

By excluding cases with any family history of asthma or those with any history of allergy, outcome of the study was refined and the beneficial effect of montelukast as controller medication of asthma was seen. Along with the

randomization process, montelukast was given to the patients within the first twelve hours after admission in the pediatric ward/emergency, so that its effect can be accessed as a true modifier of disease.

In this study, The Mean clinical severity score of patients in group A was 0.07±0.03 and in group B was 0.48±0.32 with p-value of 0.000 which is statistically significant. The mean hospital stay of patients in group A was 36.4±3.8 hours and in group B was 54.3±3.7 hours with p-value of 0.000 which is statistically significant.

In a study showed that mean clinical severity score was 0.0667±0.25371 with montelukast and 0.6833±1.02118 with placebo (p=0.002) and the mean hospital stay was 37.60±15.73 hours with montelukast and 59.2±19.58 hours with placebo (p=0.002)[12].

CONCLUSION

Montelukast can be recommended to physicians treating bronchiolitis patients. It can significantly reduce the signs and symptoms of the disease, thus decreasing the disease severity along with the stay in the hospital. Study should be done on a larger population in various cities of our country to see the effect of montelukast on various populations.

REFERENCES

1. Han J, Jia Y, Takeda K, et al. Montelukast during primary infection prevents airway hyperresponsiveness and inflammation after reinfection with respiratory syncytial virus. Am J Respir Crit Care Med. 2010;182(4):455-463. doi:10.1164/rccm.200912-1811OC
2. Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. Lancet. 2017;389(10065):211-224. doi:10.1016/S0140-6736(16)30951-5
3. Jartti T, Smits HH, Bønnelykke K, et al. Bronchiolitis needs a revisit: Distinguishing between virus entities and their treatments. Allergy. 2019;74(1):40-52. doi:10.1111/all.13624
4. Kliegman RM, Staton BF, GemeJW, SchorNF.Nelson textbook of pediatrics. 20th edition. Reed Elsevier India Private Limited:Elsevier.2016;391.2047-2048.
5. Roqué i Figuls M, Giné-Garriga M, Granados Rugeles C, Perrotta C, Vilaró J. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. Cochrane Database Syst Rev. 2016;2(2):CD004873. Published 2016 Feb 1. doi:10.1002/14651858.CD004873.pub5
6. Hussein HR, Gupta A, Broughton S, Ruiz G, Brathwaite N, Bossley CJ. A meta-analysis of montelukast for recurrent wheeze in preschool children. Eur J Pediatr. 2017;176(7):963-969. doi:10.1007/s00431-017-2936-6
7. Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. Pharmacol Res Perspect. 2017;5(5):e00341. doi:10.1002/prp2.341
8. Gaffin JM, Phipatanakul W. The Calculated Risk of Childhood Asthma From Severe Bronchiolitis. J Allergy Clin Immunol Pract. 2017;5(1):97-98. doi:10.1016/j.jaip.2016.10.015
9. Amirav I, Luder AS, Kruger N, Borovitch Y, Babai I, Miron D, Zuker M, Tal G, Mandelberg A. A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. Pediatrics. 2008;122(6):1249-55.
10. Zedan M, Gamil N, El-Assmy M, Fayez E, Nasef N, Fouda A, Settin A. Montelukast as an episodic modifier for acute viral bronchiolitis: a randomized trial. In Allergy and asthma proceedings 2010;31(2):147-153.
11. Kearns GL, Lu S, Maganti L, Li XS, Migoya E, Ahmed T, Knorr B, Reiss TF. Pharmacokinetics and safety of montelukast oral granules in children 1 to 3 months of age with bronchiolitis. The Journal of Clinical Pharmacology. 2008;48(4):502-11
12. Hameed MN, Sattar SA,Hussain W. Montelukast an Effective and Simple Therapeutic Option In Bronchiolitis: Pak Pead J 2014;38(4):229-34.