

Acute Bronchiolitis Treatment: A Comparison of Montelukast, Aminophylline and Ventolin in Pediatric Patients: A Clinical Trial Study

Gholamreza Soleimani¹, Elham Shafighi Shahri², *Seyed Hosein Soleimanzadeh Mousavi³

¹Associate Professor of Pediatric Infectious Disease, Department of Pediatrics, School of Medicine, Children and Adolescents Health Research Center, Research Institute for Drug Resistant Tuberculosis, Ali-Ibn-Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran. ²Assistant Professor of Pediatrics, Department of Pediatrics, School of Medicine, Children and Adolescents Health Research Center, Research Institute for Drug Resistant Tuberculosis, Ali-Ibn-Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran. ³Resident of Pediatrics, Department of Pediatrics, School of Medicine, Ali-Ibn-Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran.

Abstract

Background: The effects of various drugs on reducing the severity of bronchiolitis symptoms in children have been identified. We sought to make a comparison of Montelukast, Aminophylline and Ventolin (Intravenous Salbutamol) in the treatment of acute bronchiolitis in patients ranged between 1 and 24 months old.

Materials and Methods: This study used a randomized clinical trial method. Statistical population of the study included all patients younger than 2 years and older than one month who were admitted to Ali-Ibn-Abitaleb Hospital in Zahedan-Iran. Two hundred patients were divided into four groups using a random number table method. The first group received supplemental monotherapy with Montelukast 4 mg/kg daily for 7 days. The second group received 1 mg/kg Aminophylline injection every 12 hours. The third group or the control group received supportive measures. The fourth group received 0.15 mg/kg Ventolin Nebules with dose of 2.5 mg. Symptoms were measured on days 2, 5 and 7, and the number of hospital admissions days was also assessed in four groups and compared.

Results: The results showed that the consumption of Montelukast and Ventolin Nebules had no significant effect on bronchiolitis treatment in comparison with the control group ($P>0.05$). Using Aminophylline did not reduce the symptoms of bronchiolitis in comparison with the control group ($P<0.05$). The results also showed that using aminophylline in group B did not produce better results in decreasing the severity of the symptoms of bronchiolitis in comparison with Montelukast group and Ventolin group ($P<0.05$).

Conclusion

The results showed that consumption of Aminophylline, Montelukast and Ventolin had no significant effect on bronchiolitis in comparison with the control group.

Key Words: Aminophylline, Bronchiolitis, Montelukast, Pediatric, Ventolin.

*Please cite this article as: Soleimani Gh, Shafighi Shahri E, Soleimanzadeh Mousavi SH. Acute Bronchiolitis Treatment: A Comparison of Montelukast, Aminophylline and Ventolin in Pediatric Patients: A Clinical Trial Study. *Int J Pediatr* 2021; 9(6): 13683-690. DOI: **10.22038/IJP.2020.51086.4055**

*Corresponding Author:

Seyed Hosein Soleimanzadeh Mousavi, Department of Pediatrics, School of Medicine, Ali-Ibn-Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran.

Email: Dr_soleimanzadeh@yahoo.com

Received date: Jun.23, 2020; Accepted date: Feb.22, 2021

1- INTRODUCTION

Acute bronchiolitis is a common infection of lower respiratory tract worldwide (1). Bronchiolitis is the cause for 18 to 75 thousand hospitalizations (2). Although the severity of acute bronchiolitis is related to the small bronchi inflammation rate, it also involves the upper respiratory tract, which results in nasal congestion, lack of adequate feeding, dehydration, respiratory distress and sometimes hypoxia (3). The mortality rate is less than 1% and the major causes of death are sleep apnea, uncompensated respiratory acidosis and severe dehydration (4). Risk factors such as congenital heart disease, bronchopulmonary dysplasia and immunodeficiency increase the severity of the disease. The most frequent etiology is the respiratory syncytial virus (RSV), and 80% of cases occur during the first year of life, with the peak point of incidence being 2 to 6 months of age and maximum age which is involved is two years old (5).

Bronchiolitis usually occurs after contact with an adult with upper respiratory tract infection one week before disease presentation. The most common presentations are sneezing, runny nose, loss of appetite, mild fevers (6), respiratory distress symptoms (coughs, shortness of breath, restlessness and tachypnea), and apnea (in infants younger than 2 months and premature) (7). Common physical examination findings are fine crackles or sometimes obvious wheezes, increased expiratory phase, respiratory distress symptoms (intercostal muscles retraction), chest x-ray changes (10-30% are normal) (6), hyperinflation (7), segmental density in 8-20% of cases and rarely pleural effusion has been reported (8). In the majority of cases, para-clinical tests show normal results. Sometimes increased white blood cell count with normal or neutrophils/mononucleosis differential count predominance is seen.⁸ Diagnosis is based on clinical findings, which is

determined as the first attack of wheezing (dyspnea) in a previously healthy infant, and reaching the diagnosis requires no laboratory or radiological investigations (8). According to studies, treatment is often based on supportive care including adequate oxygenation (in case of oxygen saturation less than 90%) (8), the semi-sitting position at an angle of 30 degrees, using nasogastric tube for feeding, hydration, the support of airways protection through an endotracheal tube and mechanical ventilation and, if needed, frequent nose and mouth secretions suctioning (2, 7). Administration of bronchodilators showed useful effects in improving clinical symptoms. Using antibiotics has no place in the treatment of this disease. Among the other drugs currently used in articles, we can mention Montelukast, nebulizer by Ventolin. Some articles have also used Aminophylline. Farrahnaz et al. (2012) studied 100 patients with a mean age of 3 months who underwent Aminophylline treatment and showed improved clinical severity score in the third day of treatment, but there was no difference in the score and hospitalization duration between the two groups of patients and cases in the fifth day (16). Zou et al. investigated 75 neonates in China divided into two groups, with one of the groups being treated with 4 milligrams of Montelukast/daily for 7 days. After treatment, urine level of interleukin B4 and interleukin E4 showed significantly lower levels in the group treated with Montelukast. Not only bronchiolitis symptoms such as coughing, wheezing but also hospitalization duration in the group treated with Montelukast decreased (13). Another study was conducted by Wang et al. (2017) to observe the effects of Montelukast combined with Pidotimod on acute phase protein (APP) and indexes of immunologic function in pediatric acute bronchitis treatment. A total of 180 children with acute bronchitis were studied as the research subjects. The results

showed that using Montelukast combined with Pidotimod can effectively reduce the children's acute phase protein levels and improve immune function, which has clinical value for the treatment of children with acute bronchitis (9). Given the high prevalence of acute viral bronchiolitis in neonate populations and potential morbidity effects, this study seemed to be necessary in pediatric patients and more in younger children because they are a more sensitive group. Therefore, providing further clues in viral bronchiolitis management, we aimed at undertaking a prospective, single-center, randomized controlled trial to evaluate the efficacy of Montelukast compared with Aminophylline and Ventolin in the treatment of bronchiolitis in pediatric patients.

2- MATERIALS AND METHODS

2-1. Study design and population

This research was a randomized clinical trial. The statistical population of the study included all the patients ranged between 1 and 24-months old who were admitted to Ali-Ibn-Abitaleb Hospital in Zahedan in a period of one year (2018), and who were admitted to the infectious ward by diagnosis of bronchiolitis and met the inclusion criteria.

2-2. Methods

All infants from 4 weeks to 24 months of age with the first wheeze attack and onset of bronchiolitis diagnosis who required hospitalization and oxygen reception with a minimum score of 4 based on the clinical bronchiolitis severity score (CBSS) (21) were included in the study.

2-3. Measuring

An available sampling method was used. Patients were scored on the basis of clinical scores, and those who scored more than 4 were included.

2-4. Intervention

Patients were randomly divided into 4 groups of 50. For all patients in the 4 groups, a researcher-made form included the following information: file number, family name, age, sex, and first sign at the time of admission, type of nourishment, changes in blood tests of the patient, changes in gradients and CBSS findings (21) after treatment on days 2, 5 and 7. Patients who met the inclusion criteria for entry and whose symptoms corresponded to the clinical diagnosis of bronchiolitis were divided into three groups after being admitted to the hospital: mild ($RR < 30$), moderate ($RR = 30-60$), and severe ($RR > 60$) (21). Patients in the moderate group were divided into 4 groups using a random number table method, and 200 children (according to latest studies) from each group were evaluated. Groups A, B, C and D received Montelukast, Aminophylline, supportive treatment and Ventolin, respectively. Then, their clinical status, respiratory rate, inter-ridge transplantation, dyspnea and wheeze were evaluated before and after treatment on days 2, 5 and 7. The first group received supplemental monotherapy with Montelukast 4 mg daily for 7 days. The second group received 1 mg/kg Aminophylline injection every 12 hours. The third group (the control group) received supportive treatment. The fourth group received 0.15 mg/kg Ventolin Nebulizer with minimum dose of 2.5 mg. Symptoms were measured on days 2, 5 and 7, and the number of hospital admission days was also assessed.

2-5. Inclusion and exclusion criteria

Inclusion criteria in this study were: child younger than 2 years old, a brief description of the recent upper respiratory tract infection that had led to the formation of a wheeze or crackle in the lung with a clinical diagnosis of bronchiolitis, having CBSS 4-8 three times at the time of admission. Exclusion criteria were: age of younger than 1 month or older than 2

years, a biography of frequent wheeze attacks, severe neurological disease, Immunodeficiency, congenital heart disease, prematurity in pregnancy history (gestational age less than 34 weeks), a birth weight of less than 2500 gr, an oxygen saturation percentage of less than 85% in room air, a CBSS-10 of less than 4 or more than 8, unstable vital signs (a heart rate of greater than 200 per minute, a blood pressure of 2 or higher than normal for age and sex, a respiratory rate of greater than 70 per minute), existence of foreign body and reflux.

2-6. Data Analyses

Repeated measures ANOVA was also used to analyze the data. Post hoc Scheffe test

was run to examine the effect of grouping. SPSS software version 21.0 was used to do the statistical analysis. P-value less than 0.05 was statistically significant.

3- RESULTS

The mean age was 6.17 ± 3.45 months. 140 of them were male and 60 were female. The mean age in groups A, B, C and D were 5.98 ± 2.58 , 5.36 ± 2.37 , and 7.20 ± 4.96 and 6.14 ± 3.12 months, respectively. The male to female ratio of groups A, B, C and D were 35/15, 36/14, 37/13 and 32/18, respectively. The results of the repeated measures ANOVA in **Table.1** show a significant difference in the received medicine by different groups over time ($F=39.05$, $P<0.05$).

Table-1: Results of Repeated Measures ANOVA.

Source	Sum of Squares	df	Mean Square	F	P-value
Intercept	260.042	1	260.042	325.370	*0.000
Group	93.645	3	31.215	39.057	*0.000
Error	156.647	196	0.799		

* $P<0.05$. df: Degree of freedom.

The results of post hoc Scheffe test in **Table.2**, showed that consumption of Montelukast and Ventolin had no significant effect on bronchiolitis in comparison with the control group. However, the results showed that using Aminophylline did not improve the symptoms of bronchiolitis in comparison

with the control group ($P<0.05$). The results also showed that using Aminophylline in group B did not produce better results in decreasing the severity of the symptoms of bronchiolitis in comparison with the A and D groups ($P<0.05$). These cases are shown schematically in **Figure.1**.

Table-2: Results of post hoc Scheffe Test.

Groups		Mean Difference	Std. Error	P-value
A	B	-0.96	0.103	*0.000
	C	-0.26	0.103	0.087
	D	-0.04	0.103	0.977
B	A	0.98	0.103	*0.000
	C	0.72	0.103	*0.000
	D	0.94	0.103	*0.000
C	A	0.26	0.103	0.087
	B	-0.72	0.103	*0.000
	D	0.22	0.103	0.212
D	A	0.04	0.103	0.977
	B	-0.94	0.103	*0.000
	C	-0.22	0.103	0.212

* $P<0.05$. A: Montelukast group, B: Aminophylline group, C: Control group, D: Ventolin Nebules group.

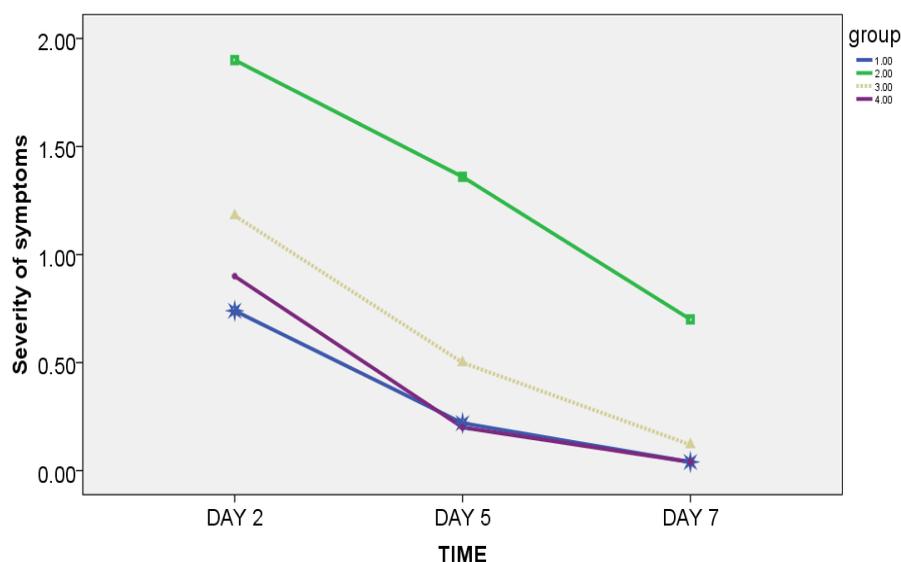


Fig.1: Severity of bronchiolitis symptoms after taking different medications.

4- DISCUSSION

The present study aimed to compare the effects of Montelukast, Aminophylline and Ventolin in the treatment of acute bronchiolitis in pediatric patients. The results showed that consumption of Montelukast and Ventolin had no significant effect on bronchiolitis in comparison with the control group. Acute bronchitis is a common respiratory disease in pediatrics. The incidence of pediatric respiratory disorder shows a higher risk due to the special physiological and anatomic structure of the respiratory system and vulnerable immune function of children. This disease is caused by a bronchial mucosal inflammatory response which is initiated by inflammatory cells such as eosinophil and neutrophils, more secondary to upper tract respiratory infections. If the treatment is not timely or prompt, it may lead to pulmonary heart disease, emphysema and other serious complications, and even threaten children's health (10, 11). The incidence of acute bronchitis is often accompanied by the occurrence of wheezing symptoms, and the mechanism of acute bronchitis is similar to asthma, namely airway smooth muscle

contraction caused by a variety of inflammatory factors (12). Clinical treatments of children with acute bronchitis often focus on controlling infection and symptomatic treatment. However, treatment for long periods of time may cause side effects and relapse because of its long duration and is easily repeated after discontinuance (9). Montelukast is a leukotriene receptor inhibitor. Relevant studies have showed that it can inhibit the inflammatory factors, cytokines and the release of respiratory leukotrienes, etc. to improve the high airway response.¹³ Related studies have found that Montelukast can effectively shorten the treatment process of acute bronchitis, and effectively relieve wheezing and other symptoms. (9, 14, 15). Regarding using Ventolin nebulizer, this study showed that there was no significant effect on decreasing the severity of symptoms of bronchiolitis in comparison with the control group ($p > 0.05$). Farrahnaz conducted a study to evaluate the effectiveness of nebulized mucolytic therapy (N-acetyl cysteine) in the treatment of children with acute bronchiolitis. All the patients aged 2 months to 24 months who were diagnosed

with acute viral bronchiolitis entered the study. All eligible patients were randomly assigned to one of the two groups: group-1 received N-acetyl cysteine in nebulized form, and group-2 received salbutamol as a nebulized aerosol. Both groups were then compared regarding their clinical improvement and duration of stay in the hospital. On the basis of improvement in clinical severity score and early discharge from the hospital, N-acetyl cysteine was found to be an effective therapy in acute bronchiolitis (16). But the interesting result was that using Aminophylline had a significant effect in comparison with the other three groups, but this effect did not reduce the severity of bronchitis symptoms ($p < 0.05$).

In a randomized controlled study, Ream et al. found that Aminophylline administration added to an aggressive regimen of inhaled and intravenous (IV) β -agonist, inhaled ipratropium, and IV methylprednisolone led to a significant decrease in the time needed to resolve symptoms (as measured by improvement in a clinical evaluation score). The authors did not find a significant decrease in either pediatric critical care unit or hospital length of stay (17). In another randomized trial, Yung et al. found no significant difference in pediatric critical care unit length of stay between the group receiving Aminophylline and the one receiving placebo in a subset of patient's admitted to the pediatric critical care unit (18).

In a recent review of fifteen randomized controlled trials by Nair et al., the authors concluded that there was no statistical significant difference between bronchodilation effects of Aminophylline when added to standard care with inhaled beta-2-agonists. They also concluded that the risk benefit balance of Aminophylline was unfavorable due to a high rate of complications (19). In line with Abdallah et al., it can be concluded that the addition of Aminophylline to therapy can be

associated with statistically and clinically significant increases in functional length of stay and time to symptoms improvement in the pediatric critical care unit (20). This potential morbidity supports the National Asthma Education and Prevention Program guideline proscribing Aminophylline use in acute bronchiolitis.

4-1. Study Limitations

One of the limitations of the study is the early discharge of patients with personal consent and the lack of cooperation of families in continuing treatment. Another example of limitation in the present study was the lack of complete familiarity of families and the lack of sufficient cultural level in them to participate in the study.

5- CONCLUSION

Regarding the recent studies, it has been shown the consumption of Montelukast, Ventolin and Aminophylline had no significant effect on bronchiolitis treatment compared with the supportive therapies. This study showed treatment by Aminophylline in bronchiolitis was associated with an increase in both the length of hospitalization and treatment duration in pediatrics. Despite the use of Ventolin and Montelukast in treatment of bronchiolitis that caused a decrease in treatment duration, this decrease was not significant. In summary, the results of this study showed that there is no preference for the treatment of patients with bronchiolitis.

6- ACKNOWLEDGEMENTS

The authors thank the emergency medical service personnel, Pediatric Residents, nurses, and emergency physicians who participated in the study. This article was supported by the Children and Adolescents Health Research Centre, Zahedan, Iran.

7- AUTHOR CONTRIBUTIONS

S.H Soleimanzadeh, analyzed the data and wrote the first draft of this manuscript. Gh. Soleimani and E. Shafighi did data-cleaning and supported analysis of the data. Gh. Soleimani reviewed all statistical analyses and critically revised this manuscript. All of the authors read and approved the final manuscript.

8- CONFLICT OF INTEREST: None.

9- REFERENCES

1. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langley G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997–2006. *The Pediatric infectious disease journal*. 2012;31(1):5-9.
2. Chaudhry K, Sinert R. Is nebulized hypertonic saline solution an effective treatment for bronchiolitis in infants? Mosby; 2010.
3. Bar A, Srugo I, Amirav I, Tzverling C, Naftali G, Kugelman A. Inhaled furosemide in hospitalized infants with viral bronchiolitis: A randomized, double-blind, placebo-controlled pilot study. *Pediatric pulmonology*. 2008;43(3):261-7.
4. Zhang J, Chen F, Zhao X, Aoyama A, Okamoto T, Fujinaga T, et al. Nebulized Phosphodiesterase III Inhibitor During Warm Ischemia Attenuates Pulmonary Ischemia–Reperfusion Injury. *The Journal of Heart and Lung Transplantation*. 2009;28(1):79-84.
5. Wainwright C, Altamirano L, Cheney M, Cheney J, Barber S, Price D, et al. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *New England Journal of Medicine*. 2003;349(1):27-35.
6. Scarfone RJ. Controversies in the treatment of bronchiolitis. *Current opinion in pediatrics*. 2005;17(1):62-6.
7. Al-bahadily A-kJM, Al-Omrani AA-aM, Atiya AA. Hypertonic 3% Saline in Comparison with 0.9%(Normal) Saline in Treatment of Acute Bronchiolitis. *International Journal of Pediatrics*. 2017;5(1):4209-16.
8. Ralston S, Roohi M. A randomized, controlled trial of nasal phenylephrine in infants hospitalized for bronchiolitis. *The Journal of pediatrics*. 2008;153(6):795-8. e1.
9. Wang J, Liu C-D, Peng M-F, Ran C-P. Effects of montelukast sodium combined with pidotimod on acute phase protein and immune function in children with acute bronchitis. *Journal of Hainan Medical University*. 2017;23(16):74-7.
10. Smith SM, Smucny J, Fahey T. Antibiotics for acute bronchitis. *Jama*. 2014;312(24):2678-79.
11. Ludwig S, Stier H, Weykam S. Evaluation of blood alcohol concentrations after oral administration of a fixed combination of thyme herb and primrose root fluid extract to children with acute bronchitis. *Drug research*. 2016;66(02):69-73.
12. Kroening-Roche JC, Soroudi A, Castillo EM, Vilke GM. Antibiotic and bronchodilator prescribing for acute bronchitis in the emergency department. *The Journal of emergency medicine*. 2012;43(2):221-7.
13. Zou Y, Zhang J, Ma C, Li J, Zai J, Guo Y. Clinical efficacy of montelukast sodium in treating infantile wheezing. *Eur Rev Med Pharmacol Sci*. 2014;18(6):775-80.
14. ZW L. Clinical efficacy of montelukast sodium in the prevention and treatment of asthmatic bronchitis. *Beijing Med J*. 2016;38(7):647.
15. Nagao M, Ikeda M, Fukuda N, Habukawa C, Kitamura T, Katsunuma T, et al. Early control treatment with montelukast in preschool children with asthma: A randomized controlled trial. *Allergology International*. 2018; 67(1):72-8.
16. Naz F, Raza AB, Ijaz I, Kazi MY. Effectiveness of nebulized N-acetylcysteine solution in children with acute bronchiolitis. *Journal of the College of Physicians and Surgeons-Pakistan: JCPSP*. 2014;24(6):408-11.
17. Ream RS, Loftis LL, Albers GM, Becker BA, Lynch RE, Mink RB. Efficacy of IV theophylline in children with severe status asthmaticus. *CHEST J*. 2001;119(5):1480-88.

18. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma.

19. Nair P, Milan SJ, Rowe BH. Addition of intravenous aminophylline to inhaled beta(2)-agonists in adults with acute asthma. *Cochrane Database Syst Rev.* 2012 Dec 12;12(12):CD002742.

20. Dalabih AR, Bondi SA, Harris ZL, Saville BR, Wang W, Arnold DH. Aminophylline infusion for status asthmaticus in the pediatric critical care unit setting is independently

Archives of disease in childhood. 1998;79(5):405-10.

associated with increased length of stay and time for symptom improvement. *Pulmonary pharmacology & therapeutics.* 2014;27(1):57-61.

21. Duarte-Dorado DM, Madero-Orostegui DS, Rodriguez-Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. *J Asthma.* 2013;50(10):1056-1061.