ISSN: 2538-5887; Pathobiology Research. 2024; 27 (3): 19-29

Comparison of Efficacy of Nebulized Ventolin, Pulmicort and Normal Saline in Treatment of Infants with Bronchiolitis Admitted in Ahvaz Abuzar Hospital

ARTICLE INFO

Article Type:
Original Research

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ABSTRACT

Background: Bronchiolitis is a common lower respiratory tract infection in infants. Apart from supportive care, no effective treatment for this disease has been identified so far. Accordingly, a double-blind randomized controlled trial was conducted on infants with a diagnosis of mild to moderate bronchiolitis.

Material and Methods: Three clinical trial groups were designed, including Ventolin 0.15 mg/kg, Palmicort 125 mg twice a day, and normal saline nebulization every 4 hours. Clinical symptoms were monitored by asthma and allergy specialist daily, and the need for supplemental oxygen, recovery time from symptoms, and hospital days were recorded and compared between the three groups.

Results: The results demonstrated that the frequency of oxygen requirement in both palmicort and normal saline groups was lower in compare to the ventolin group. But there was no significant difference between the three groups (P=0.765 and P=0.907, respectively). The duration of symptom improvement in the normal saline and palmicort group was significantly shorter than the Ventolin group (P=0.017). No significant difference was observed between the three groups of Ventolin, Pulmicort and normal saline during the treatment in terms of clinical score (P≥0.05).

Conclusion: The obtained results showed that Ventolin or Palmicort nebulizer is not statistically better than normal saline for the treatment of children with bronchiolitis. Therefore, our results do not support the routine use of bronchodilators in the clinical setting for the management of mild to moderate forms of bronchiolitis in infants.

Keywords:

Bronchiolitis, Ventolin, Pulmicort, Nebulizer, Normal Saline, Infants.

Abbreviation list:

Here

INTRODUCTION

Bronchiolitis is a widespread infection of the lower airways that presents in infants aged less than two months and is the leading most cause of hospitalization for more than 50% of subjects with acute bronchiolitis aged 1 to 3 months (1). In other words, bronchiolitis is a limited infection characterized by extensive airway obstruction resulting from inflammation and severe edema, increased production and accumulation of mucus, and sloughed epithelium (2). The most critical clinical cold-like signs of acute bronchiolitis involve a fever, runny nose, dry cough, wheezing, and intensified function of breathing or tachypnea (3). Many risk factors affect the incidence of bronchiolitis, including prevalent viral infection caused by a respiratory syncytial virus (RSV), prematurity, age younger than five months and male sex, airway abnormalities, immune system disorders, chronic lung disease (bronchopulmonary dysplasia), congenital heart and neurological disorders coincided with environmental factors (3). Despite the high prevalence and numerous complications associated with bronchiolitis, no effective either short-term or long-term curative treatment guideline has been confirmed for bronchiolitis until now. Currently, the treatment of bronchiolitis is commonly based on supportive

therapies such as fluid therapy, antipyretic drugs, oxygen supplements, and emergency mechanical ventilation (1).

Recent studies have declared conflicting results on the clinical application of agonists such as Ventolin, epinephrine, and the medical advantage of beta-2 corticosteroid or bronchodilator interventions like Pulmicort (4-9). Indeed, these studies have also focused on the importance role of inhaled Ventolin, in improving oxygen saturation and heart rate in children aged under six months who have prone to respiratory distress because of small diameter airways, edema, and inflammation in the bronchioles, along with numerous neurological, cardiac, gastrointestinal side effects and drug interactions (10–11). The lack of bronchodilators capability in the bronchiolitis treatment can be depended directly upon the increased submucosal swallowing, decreased mucociliary clearance, airway obstruction following epithelial and inflammatory cell debridement, and failure to smooth muscle occlusion (12-16). Accordingly, in many medical guidelines, saline solutions have recently been recommended as a cheap, available drug without non-side effects to relieve the symptoms of bronchiolitis by absorbing water from the submucosa layer, reducing edema, improving mucociliary function, and reducing patient hospitalization days (13, 17-22). Based on the low efficacy of nebulized bronchodilators, Ventolin, and Pulmicort corticosteroid because of their numerous clinical side effects and varied acute bronchiolitis side effects, this has a disagreement on the standardized clinical practice guidelines for the diagnosis and the control of child bronchiolitis, yet (22, 23). In the case of inflammatory diseases of the respiratory system such as bronchiolitis, the mainstay of treatment is supportive care, emphasizing adequate hydration and oxygenation, with no role for the use of bronchodilators, steroids, or antibiotics. However, studies provide evidence for the efficacy of nebulized normal saline in these patients (24-26).

Hence, we designed the present study to evaluate the compared effectiveness of nebulized Ventolin, Pulmicort, and normal saline inhalation therapy in the treatment of bronchiolitis in children aged under two years.

PATIENTS AND METHODS:

Experimental pattern and subjecting technique

This research constitutes a double-blind randomized controlled trial conducted on children under the age of two who were diagnosed with various manifestations of bronchiolitis and admitted to the neonatal ward of Abouzar Hospital in Ahvaz, Iran, between March 2019 and May 2020. The study employed a power analysis and sample size calculation utilizing specialized software developed by the biostatistics department at Vanderbilt University in the United States. The criteria for inclusion in this study encompassed hospitalized children under two years old with a confirmed diagnosis of bronchiolitis, as determined by asthma and allergy specialist, while excluding those with other underlying health conditions. Exclusion criteria included chronic heart and lung diseases, such as heart failure or lung cysts, immune deficiencies, metabolic or neurological disorders, a history of preterm birth (defined as less than 34 weeks of gestation), the necessity for mechanical ventilation during infancy, and the administration of systemic or antibiotic corticosteroids during hospitalization. The ethical review board of Jundishapur University of Medical Sciences granted approval for this clinical study, and written informed consent was obtained from the parents or guardians of all participants involved in the research (IR.AJUMS.REC.1398.807). (Webpage of ethical approval code is *https://ethics.research.ac.ir/PortalProposalList.php?code=IR.AJUMS.REC.1398.807&title=&name=&stat=&isAll=*). In addition, the IRCT code (IRCT20200209046435N1) was received, as clinical trial permission (Webpage of randomized clinical trials approval code is https://irct.behdasht.gov.ir/trial/45839).

MATERIALS

The nebulizer used in this study was Accumed CO, NF100, Switzerland. The drugs such as Ventolin and Pulmicort were prepared from GSK, CO, Fance. The spirometer used during experiment was desktop spirometer, SP100, CONTEC Co., Ltd., Beijing, China.

Calculating the sample size

The sample size was determined using BIOSTAT software provided by the Department

of Biostatistics at Vanderbilt University School of Medicine, USA (https://biostat.app.vumc.org/wiki/Main/PowerSampleSize). The alpha level set at 0.05, a desired power of 0.8, a mean difference of 1.2 between the two groups in the outcome variable, and a standard deviation of 2.5 as referenced in the study by Khashabi et al (27). Accordingly, the calculated sample size was 141 participants. However, during the experiment, 36 patients were excluded, resulting in a final sample size of 105 participants, with equal distribution across the three groups.

Initial evaluation of patients

Prior to the commencement of the study, all participants underwent evaluations by specialists in asthma, allergy, or pulmonary medicine. Following these assessments, measurements of oxygen saturation using a pulse oximeter, respiratory rate, and pulse rate were conducted. Individuals diagnosed with mild to moderate bronchiolitis were included in the study based on the severity of their condition, which was determined through a modified combination of clinical scales, specifically the Yale Observation Scale (YOS) and the Respiratory Distress Assessment Index (RDAI) scores. Based on the cumulative scores from these two assessments, patients were categorized into three distinct groups: Those with mild bronchiolitis (scores ranging from 0 to 8), moderate bronchiolitis (scores from 9 to 18), and severe bronchiolitis (scores exceeding 19). Additionally, the clinical severity of bronchiolitis was evaluated alongside various clinicopathological characteristics, including age, sex, prior medical history, and patterns of wheezing disease for each patient.

Clinical interventional performance

In this double-blind study (neither the participants nor the researcher knows which treatment or intervention participants are receiving until the clinical trial is over), all infants admitted with bronchiolitis were randomly divided into three distinct groups. To facilitate this, each patient was assigned a number ranging from 1 to 141 using a random number table. The first to third clinical trial groups received nebulized Ventolin (Salbutamol) at a dosage of 0.15 mg/kg every four hours (28), 125 mg of budesonide (Pulmicort) (28) administered twice daily (morning and evening), and normal saline nebulizations (3% normal saline, 3 ml) every four hours (29), respectively. The inhaled medication was delivered via a face oxygen mask for all participants. The clinical physician determined the duration of treatment based on the clinical response and the evaluated clinical scores. The medications utilized in this study were part of the standard treatment protocol, ensuring that patients did not incur any additional costs compared to other available methods and treatments. In our research, both the parents of the children and the statistical analyses of the results were aware of the patient groupings and the allocation of patients to the treatment groups.

The evaluation of the treatment efficacy

Each patient was examined by a pediatrician in terms of the amount of oxygen saturation, the number of breaths per minute, and the number of pulses and the severity of the disease was monitored daily based on the respiratory distress assessment instrument (RDAI) which is an assessment scale to evaluate the severity of illness in infants throughout a hospitalization duration (Table 1). Clinical symptoms (wheezing, restlessness, cyanosis, retraction, dry mouth, drowsiness), need for oxygen-driven nebulizers and duration time of intravenous fluid practice, recovery time from wheezing and cough and hospital supportive care duration for all children's were recorded. Patients' clearance conditions included not requiring receiving oxygen and intravenous fluids, proper nutrition, absence or minimal wheezing, absence crackers and retraction, pulsed oxygen saturation (SpO2) of approximately 94%.

STATISTICAL ANALYSIS

The statistical analysis performed using SPSS, version 24. The normally of data assessed via Kolmogorov-Smirnov test and ANOVA test used to assess the differences between groups. Finally, the $P<0.05$ was considered as the threshold of significance.

RESULTS

Demographic and clinical characteristics of children participations

In this investigation, we included a cohort of 105 infants under the age of two who were admitted with bronchiolitis. The demographic and clinical characteristics of these participants are detailed in Table 2. there were no significant

Table 1. Evaluation of the clinical bronchiolitis severity score (CBSS).

Symptoms	Score			
	0	1	2	3
Respiratory rate (breaths per minutes)	<30	30-45	46-60	>60
Wheezing	None	Terminal expiratory or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Retraction	None	Intercostal only	Tracheosternal	Sever with nasal flaring
General condition	Normal	-	-	Irritability, lethargy, poor feeling

Table 2. Demographic and clinical characteristics of children participations across all three-trial groups. The numbers in parenthesis shows the range values and the number outside the parenthesis shows the Mean values. The comparison of groups has been done by One-Way ANOVA, and HSD post hoc test.

characteristics	Ventolin (n=35) (%)	Pulmicort (n=35) (%)	Normal saline (*n*=35) (%)	p-value
Age (months)	3 (2-6)	3 (2-5)	3 (2-6)	0.927
Gender				
boy	33(80.5)	18(54.5)	21(60)	0.166
girl	8(19.5)	15(45.5)	14(40)	
Symptoms of the disease				
wheezing	34(97.1)	35(100)	35(100)	0.364
Restlessness	21(60.0)	20(57.1)	17(48.6)	0.606
Cyanosis	1(2.9)	1(2.9)	0(0)	0.601
Retraction	33(94.3)	33(94.3)	31(88.6)	0.582
Dry mouth	6(17.1)	4(11.4)	4(11.4)	0.719
Drowsiness	2(5.7)	0(0)	0(0)	0.130
Severity disease				
Mild form	19(54.3)	22(62.9)	20(57.1)	
Moderate form	16(45.7)	13(37.1)	15(42.9)	0.760
Oxygen requirement	20(57.1)	18(51.4)	17(48.6)	0.765

differences observed among the three assigned groups concerning age at hospitalization (P=0.927) and gender distribution (P=0.166). The analysis of symptom frequency related to bronchiolitis revealed no statistically significant associations for wheezing (P=0.364), restlessness (P=0.606), cyanosis (P=0.601), retraction (P=0.584), dry mouth (P=0.719), and drowsiness rates (P=0.130) across the three groups. Furthermore, there was no significant variation in the severity of bronchiolitis associated with the subjects' hospital admissions, as shown in Table 2. Notably, a higher frequency of moderate bronchiolitis (45.7%) was observed in the group treated with Ventolin, while the Pulmicort group exhibited a greater prevalence of mild bronchiolitis (62.9%).

The effectiveness of a medical intervention based on the oxygen requirement and duration of oxygen therapy and length of hospitalization and clinical signs improvement

In the group receiving normal saline, the oxygen demand was found to be lower compared to the other two groups; however, this difference was not statistically significant (p = 0.765). There was a significant variation in the recovery time of symptoms among the three groups (P=0.017), while the duration of oxygen requirement (P = 0.097) and the length of hospitalization (P=0.228) did not show significant differences across the patient groups. Although the oxygen requirement duration in the Pulmicort and normal saline groups was lower than that in the Ventolin group (P =0.097), this finding was also not statistically

significant. Notably, the time taken for symptom improvement was significantly shorter in the normal saline and Pulmicort groups compared to the Ventolin group (P=0.017). The length of hospitalization did not exhibit any remarkable differences among the three groups (P = 0.228) (Table 3).

Table 3. Outcomes of bronchiolitis treatment in groups. The comparison of groups has been done by One-Way ANOVA, and HSD post hoc test. * vs normal saline.

characteristics	Ventolin (n=35)	Pulmicort (n=35)	Normal saline (*n*=35)	p-value
Duration of oxygen requirement (days)	2 (1-2)	1 (1-2)	1 (1-2)	**0.097**
Symptom recovery time (days)	3 (2-3)	2 (1-2)	2 (1-3)	**0.017***
Duration of hospitalization (days)	5 (4-6)	4 (4-5)	5 (4-6)	**0.228**

Data associated with comparing clinical scores and CBSS analysis

The findings presented in Table 4 indicate that during the first seven days of clinical score treatment, there were no statistically significant differences observed among the three groups (P < 0.05). However, by day 8, all patients exhibited symptom improvement, achieving a score of 0 across the groups. Additionally, the median baseline CBSS score for bronchiolitis treatment showed no significant variation among the three groups during the initial seven days. By day 8, similar to the previous observation, all groups reported symptom improvement, again resulting in a score of 0, as detailed in Tables 4.

Table 4. The median (IQR) clinical score during the treatment of bronchiolitis in all groups. The comparison of groups has been done by One-Way ANOVA, and HSD post hoc test. * vs normal saline.

Characteristics	Ventolin (n=41)	Pulmicort (n=33)	Normal saline (*n*=35)	p-value
Day1	8.0 (5.00-10.00)	8.0 (7.00-9.00)	8.0 (7.00-10.00)	0.993
Day2	6.0 (4.00-9.00)	6.0 (5.00-8.00)	6.0 (5.00-8.00)	**0.969
Day3	5.0 (3.00-7.00)	4.0 (3.00-6.00)	5.0 (3.00-7.00)	*0.831
Day4	3.0 (2.00-6.00)	3.0 (2.00-3.75)	3.0 (2.00-5.00)	0.484
Day5	4.0 (2.00-5.00)	1.5 (1.00-3.00)	3.0 (1.00-4.00)	0.102
Day6	2.0 (1.00-4.00)	3.0 (1.50-3.50)	2.0 (1.50-3.50)	0.989
Day7	2.0 (1.75-2.00)	2.0 (2.00-2.00)	2.0 (2.00-2.00)	0.607

DISCUSSION

Bronchiolitis is one of the most common respiratory infections in children under two years. So far, no effective short-term or long-term approach has been approved for bronchiolitis treatment, and current treatment is commonly supported by oxygen and fluid therapy along with emergency mechanical ventilation (30). Some antiviral agents have also been prescribed for bronchiolitis treatment even though with their ineffectiveness (31). Adverse effects of corticosteroids in terms of the treatment of bronchiolitis in many studies have also been approved. Furthermore, it was shown that the medical capability of beta-agonists such as Ventolin and epinephrine in child bronchiolitis can be corresponded to short-term improvement, but their influenced effectiveness has not yet been determined (32). Subsequently, it clearly revealed that the use of bronchodilators reduces the clinical signs of bronchiolitis, but due to the greatest underlying causes, including high cost, low accessibility, and related side effects, more work is needed for detection of a serial of effective, available and safe drugs (33-35). Currently, the usefulness of expensive and effectiveness Ventolin and Pulmicort drugs compared to normal saline is not well evaluated that present randomized controlled trial of double-blind was carried out with the aim of efficacy investigating of Ventolin, Pulmicort, normal saline therapy for child bronchiolitis

survey in kids less than two years.

In this study, the three groups of Ventolin, Pulmicort, and normal saline were not significantly different in terms of age, sex, and type of early symptoms (wheezing, restlessness, cyanosis, retraction, dry mouth, drowsiness) and the severity of the disease at the beginning of hospitalization. This study showed that the frequency of oxygen requirement in the normal saline group was lower than the other two groups. However, there was no significant difference between the three groups. Also, the duration of oxygen requirement in the two groups of normal saline and Pulmicort was shorter than the Ventolin group, although this difference was not statistically significant. Moreover, the duration of symptom recovery in the two groups of normal saline and Pulmicort was significantly shorter than in the Ventolin group. The duration of symptom improvement did not show a significant difference between the two groups of Pulmicort and saline. Also, no significant difference was observed in the length of hospitalization between the three groups. Overall, these results show that the treatment results with Pulmicort and normal saline are almost similar and somewhat better than the Ventolin group.

In a study by Anil et al., five different treatments for children bronchiolitis under two years of age, including normal saline, Ventolin plus normal saline, Ventolin plus 3% hypertonic saline, epinephrine + 3% hypertonic saline and epinephrine + normal saline were applied. Patient characteristics (clinical score, heart rate, and oxygen saturation) were similar at the beginning of the study in all five groups (36). Accordingly, there was not identified any critical difference between the treatment outcomes in the all studied groups, which was revealed similar effectiveness compared to generalized saline therapy in bronchiolitis cases consistent with our acquired data.

In addition, the results of some previous studies (37-41) have shown better efficacy of hypertonic saline solutions than bronchodilators. On the other hand, several researches (36, 42-44) also reported efficacy of different therapy in terms of hospital stay days, score clinical intensity, oxygen saturation, side effects, aggravation of symptoms or re-hospitalization similar to hypertensive saline 3% and normal saline therapy in hospitalized subjects with mild to moderate forms of bronchiolitis. Although the effectiveness of hypertonic saline has not been calculated in the current study, but it can be concluded that the mentioned treatments are not superior to normal saline.

The results of this study showed that during the treatment period, clinical severity scores and CBSS score were not significantly different between the three groups. Also, clinical scores improved daily during hospitalization in all three treatment groups, and the symptoms of all patients generally disappeared on day 8, while in the study of Flores et al (36) children with mild to moderate bronchiolitis treated with hypertonic saline and normal saline, had an increased disease severity in the first and second days of scurvy contrary to our results. This discrepancy may be correlated to differences in patient's baseline characteristics, such as age ranged lower than 12 months. There was a direct and significant relationship between disease severity and oxygen saturation. In other studies, patients with higher average clinical scores were a greater need for different modes of oxygen supplementation.

In a meta-analysis by Green et al., the efficacy of inhaled steroids in recurrence of wheezing after bronchiolitis in children less than 24 months of age was evaluated, and the results showed that there was no significant difference in the recurrence of wheezing or asthma with or without steroid therapy. Therefore, inhaled steroids such as Budesonide for the treatment of bronchiolitis are not effective in preventing the recurrence of wheezing or asthma (45). In another study, Cade et al. examined the effectiveness of budesonide nebulizer in treating acute viral bronchiolitis. The results showed that administration of the corticosteroid budesonide compared with placebo (sodium chloride) had no significant effect on length of hospital stay, the recovery time of symptoms, and readmission rate in children with acute viral bronchiolitis (46). Although the recurrence of symptoms such as wheezing was not investigated in the present study, these results are consistent with the findings of the present study in terms of the ineffectiveness of corticosteroids for the treatment of bronchiolitis compared to controls. In another study with Lan and collagenous (47) were found significantly reduction episodes and wheezing recurrence episodes after a course of inhaled flixotide and Pulmicort corticosteroids within one year follow

up. It is valuably noticeable that there are no universally accepted guidelines on bronchiolitis; different selected populations were assessed on the children under 6 or12 months of age and up to 24 months of life, so in this study, children were selected from 2-24 months of age. Multiple clinical trial data also indicated that beta-agonistic Ventolin therapy for bronchiolitis in child's lead to a lack of effectiveness. For example, the results of a study by Ipek et al. examining the efficacy of nebulizers salbutamol, hypertonic saline 3%, and normal saline in the treatment of bronchiolitis in children showed that there was no significant difference between the efficacy of the treatments and salbutamol had no additional effect on recovery compared to normal saline. There were no symptoms (CBSS score) in children with bronchiolitis (48). In other studies, Kamali Aqdam (49) and Zamani et al (50) were reported an improved clinical symptom, and reduced hospital stay days related to acute bronchiolitis with hypertensive inhalation saline therapy better than the nebulized ventolin. Other therapeutic options, including the effective salbutamol and epinephrine nebulizer's treatment in relieving symptoms, reducing respiratory distress, and improving oxygenation in children with bronchiolitis, may be superior to 9% hypertonic saline. Totally, some studies (47, 54) showed the superiority of beta-agonists over normal saline, and other research, like the present study, resulted that these drugs are not effective for acute bronchiolitis because of differences in the disease severity, patient characteristics, and the clinical scores used for the disease severity and the symptoms measuring. In addition, the normal course of this disorder and its pathophysiology could be associated to diverse from several viral agents with separated therapeutic effects. However, a definite conclusion in this regard requires further multicenter studies with higher sample size. Annual hospitalization for bronchiolitis is costly for health care systems and patients; because treatment-independent bronchiolitis improves spontaneously, it is essential to optimize and select powerful treatment interventions. Therefore, further studies are influential in distinguishing the actual treatment for children and infants with bronchiolitis and reduce useless and adverse effect processing interventions as well as decline treatment costs. Finally, the present study expressed that the administration of normal saline nebulizers for the treatment of bronchiolitis is at least as effective as Pulmicort and is more effective than Ventolin. Therefore, normal saline is not just a placebo, which has been offered in other studies. The limitations of our study included no review of long-term medication, recurrence of symptoms, re-hospitalization, severity and viral factors of bronchiolitis, and the small number of samples in each group and centralized of the study, which limits the generalizability of the results.

CONCLUSION

Consciously, none of the studied treatments is preferable to normal saline for treating mild to moderate bronchiolitis; therefore, the use of bronchodilators routinely in the clinical field is not recommended for the management of bronchiolitis. It is best to use a normal saline nebulizer as an alternative to clinically available bronchodilators such as Pulmicort (corticosteroids) and Ventolin (agonist beta) to reduce the high cost of treatment and their possible side effects. The limitations of the current study include lack of examining the infant's nutrition (Breast milk or Formula) and exposure to allergens or respiratory toxins such as cigarette smoke. Further studies are proposed to confirm our results besides investigating the effectiveness of different saline solutions with higher concentrations in children with severe bronchiolitis compared to other available bronchodilators.

ACKNOWLEDGMENTS

We would like to appreciate of all our contributors at the asthma and allergy department of Abouzar Hospital affiliated to Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran for assisting and facility experimental performing in the present study. This study was supported by grant from Jundishapur University of Medical Sciences, Ahvaz, Iran (APRD-9813), Webpage of ethical approval code is *https://ethics.research.ac.ir/PortalProposalList.php?code=IR.AJUMS.REC.1398.807&title=&name=&stat=&isAll=*

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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