# The Effect of Hypertonic Saline in Treatment of Moderate Bronchiolitis in Children

**Alaa Jumaah Nasrawi, College of Medicine, University of Kufa, alaajumaah80@gmail.com**

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## ABSTRACT

**Background**: Airway oedema and mucus plugging are the predominant pathological features in infants with acute viral bronchiolitis. Nebulized hypertonic saline (HS) solution may reduce these pathological changes and decrease airway obstruction.

**Aim**: To assess the effects of nebulized hypertonic (3%) saline solution in infants with acute viral Bronchiolitis of moderate severity.

**Methods**: This study was conducted in Al Zahraa teaching hospital for maternity and pediatric in the period between December 2013 till November 2014 at which 165 patients with acute viral bronchiolitis were included. The inclusion criteria were; Infants aged ≤18 months presented with a prodromal history consistent with viral upper respiratory tract infection followed by wheezing and/or crackles on auscultation. Patients were excluded from the study if they have the following criteria: born at ≤ 34 weeks' gestation, previous history of wheezing, steroid use within 48 hours of presentation, history of apnea within 24 hours before presentation, oxygen saturation ≤85% on room air at the time of recruitment, history of a diagnosis of chronic lung disease, congenital heart disease, or immunodeficiency, consolidation or atelectasis on a chest X-Ray and infants with bronchiolitis severity score <4 or > 8. Result: We found that nebulized 3% HS decreases bronchiolitis severity score after 12h of treatment and its effect subsided after more than 48 h. In regard to hospital stay, the study shows a decrease in mean of hospital stay length from 42.2 to 36.3 h. **Conclusion**: Nebulization with 3% hypertonic saline is safe, can be widely generalized, and may be superior to current treatment for early outpatient treatment of bronchiolitis.

**Recommendation**: Planning for a multicenter trial to explore the clinical benefit of this therapy with a large sample size is essential.

## Introduction

Bronchiolitis is defined as inflammation of the bronchioles, usually is caused by an acute viral infection [1]. Respiratory syncytial virus (RSV) causes 20-40% of all cases and 44% of cases that involve children younger than 2 y. Two RSV subtypes, A and B, were identified on the basis of structural variations in the G protein. Subtype a causes the most severe infections. One subtype or the other usually predominates during a given season; thus, RSV disease has “good” and “bad” years [2-5]. Other agents include parainfluenza, adenovirus, and mycoplasma. Emerging pathogens include human metapneumo virus and human boca virus, which may be a primary cause of viral respiratory infection or occur as a co-infection with RSV [6]. Bronchiolitis is a significant cause of respiratory disease worldwide. According to the World Health Organization bulletin [7], an estimated 150 million new cases occur annually; 11-20 million (7-13%) of these cases are severe enough to require hospital admission. Worldwide, 95% of cases occur in developing countries. In the United States in 2002, 149000 patients with bronchiolitis required hospitalization, with a mean hospital stay of 3.3 days and admission costs of $500 million [8]. RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over 4-5 month [9]. Risk factors for the development of bronchiolitis include the following [10-13]: 1)Low birth weight, particularly premature infants [14] , 2)Gestational age ,independently associated with hospital resource use and outcome among infants hospitalized for RSV infection, 3)Low socioeconomic group [15], 4)Crowded living conditions, daycare, or both, 5)Parental smoking [16], 6)Chronic lung disease, particularly bronchopulmonary dysplasia, 7)Severe congenital or acquired neurologic disease, 8)Congenital heart disease (CHD) with pulmonary hypertension [17]; however, a study of Swiss children with CHD did not show increased risk [18], 9)Congenital or acquired immune deficiency diseases, 10) Age less than 3 months, 11)Airway anomalies.

Acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucus, and cellular debris. Even minor bronchiolar wall thickening significantly affects airflow because the resistance is inversely proportional to the 4th power of the radius of the bronchiolar passage. The resistance in the small air passages increases during both inspiration and exhalation, but because the radius of an airway is smaller during

expiration, the resultant respiratory obstruction leads to early air trapping and over inflation. If obstruction becomes complete, trapped distal air will be resorbed and the child will develop atelectasis. Hypoxemia is a consequence of ventilation-perfusion mismatch early in the course. With severe obstructive disease and tiring of respiratory effort, hypercapnia can develop [6].

Over a period of 2-5 days, RSV infection progresses from the upper to the lower respiratory tract, and this progression leads to the development of cough, dyspnea, wheezing, and feeding difficulties. When the patient is brought to medical attention, the fever has usually resolved. Severe cases progress to respiratory distress with tachypnea, nasal flaring, retractions, irritability and possibly cyanosis [19]. With bronchiolitis, as with any disease, various complications are possible, including those caused by therapy. In most cases, the disease is mild and self-limited. However, in infants who are immune suppressed and those with preexisting heart or lung disease, RSV bronchiolitis can result in acute respiratory distress syndrome (ARDS), bronchiolitis obliterans, congestive heart failure, secondary infection, myocarditis, arrhythmias or chronic lung disease [20-22].

The diagnosis of bronchiolitis is based on clinical presentation, the patient's age, seasonal occurrence, and findings from the physical examination. When the suspension of bronchiolitis is high, few laboratory studies are necessary [23]. According to a survey of hospital-based pediatricians, the most common tests are rapid viral antigen testing of nasopharyngeal secretions for RSV, arterial blood gas (ABG) analysis (in severely ill patients, especially those requiring mechanical ventilation), white blood cell (WBC) count with differential, C-reactive protein (CRP) level, and chest radiography [24].

Despite the high prevalence and morbidity of bronchiolitis, therapy remains controversial and without widely accepted therapeutic guidelines other than supportive care [25, 26]. Bronchiolitis is characterized by airway plugging with sloughed epithelium, mucus, and edema rather than bronchospasm [27, 28]. Nevertheless, the use of nebulized bronchodilators continues to be common [29, 30] despite extensive evidences supported by 3 meta-analyses that the benefits are limited, short term, and do not justify routine use [31-33]. Similarly, although steroids might reasonably be expected to decrease the inflammatory response in bronchiolitis, published data are conflicting, with equally

well-designed studies concluding that steroids may be either effective [34-36] or ineffective [37-39]. The primary treatment, therefore, remains largely supportive, with administration of fluids and supplemental oxygen, observation, and mechanical ventilatory support as needed [26, 40].

Several reports over the last decade have demonstrated that inhalation of nebulized 6% to 10% hypertonic saline (HS) improves both immediate and long-term clearance of small airways in patients with cystic fibrosis [41-44]. The exact mechanism is unknown but is thought to facilitate removal of inspissated mucus through osmotic hydration, disruption of mucus strand cross-linking, and reduction of mucosal edema [45, 46]. Nebulized hypertonic saline have been used for treating hospitalized, as well as ambulatory, children with viral bronchiolitis, with varying degrees of success [47, 48].however; a multicenter trial with a larger sample size may help establish the clinical benefits of this therapy. The purpose of the present study was to investigate the addition of frequently nebulized 3% HS to standard therapy of moderately ill infants hospitalized with typical viral bronchiolitis in a prospective, randomized, double-blind, controlled fashion.

## Methods

This study was carried out in Al Zahraa teaching hospital for maternity and pediatric in the period between December2013 till November 2014 at which165 patients were included. The inclusion criteria were infants aged ≤18 months presented with a prodromal history consistent with a viral upper respiratory tract infection followed by wheezing and/or crackles on auscultation and a Wang [49] bronchiolitis severity score of ≥4 on presentation.

The enrolled patients were evaluated in the first hour of admission to be fitted with the inclusion criteria in addition to chest X-ray and pulse oximeter measurement. The confirmation of viral etiology was not necessary for the study inclusion because it is not routinely recommended in our center guidelines. Patients were excluded from the study if they have the following criteria: born at ≤34 weeks' gestation, previous history of wheezing, steroid use within 48 hours of presentation, obtundation and progressive respiratory failure requiring intensive care unit (ICU) admission, history of apnea within 24 h before presentation, oxygen saturation ≤ 85% on room air at the time of recruitment, history of a diagnosis of chronic lung disease, congenital heart disease, or immunodeficiency, consolidation or atelectasis on a chest roentgenogram and

infants with bronchiolitis severity score < 4 or > 8.

According to the inclusion criteria, the 165 healthy infants diagnosed with viral bronchiolitis, of median age 7.2 months (2-14 months) were randomly categorized into two groups, test group (84; 48 male & 36 female) was treated with nebulized 3% hypertonic saline (4 ml) plus 0.15 mg/kg salbutamol and the control group (81, 45 male & 36 female) was received 0.9% saline plus 0.15 mg/kg salbutamol. Patients in each group received 3 treatments every day, delivered at intervals of 8 h, until discharge using air-compressed nebulizers in addition to other treatment lines such as IV fluid, oxygen and may be antibiotics. The enrolled patients were assessed for the followings outcomes:

- Improvement in clinical severity score.
- Improvement in oxygen saturation.
- Length of hospital stay.

A written consent were obtained from the family before participation in the study. Data were collected and analyzed by Microsoft excel 2010 and IBM SPSS version 20.

## Results

The demographic characteristics and clinical measurements test and control groups were stated in the table1. The results of nebulized hypertonic saline were studied as the followings:

**Bronchiolitis severity score**: as mentioned in table 2.

**Oxygen saturation** as described in table 3.

**Length of hospital stay** as illustrated in fig 1 and table 4.

**Table 1**

Baseline characteristics of enrolled infants.

| Characteristics | Test group | Control group |
|---|---|---|
| Age (months) | 8±3.4 (3-14) | 6.5±3.3 (2-14) |
| Male/female | 1.3/1 | 1.25/1 |
| Baseline severity score | 4.8±0.6 (4-6) | 5±0.6 (4-6) |

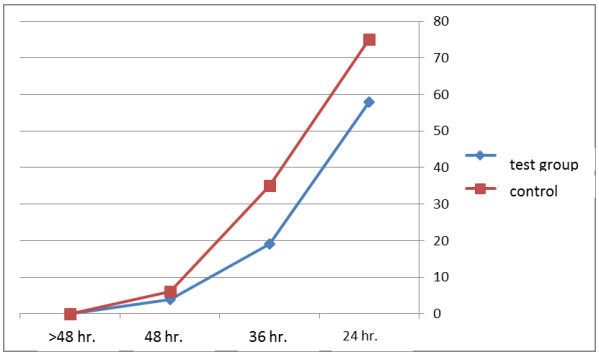


**Figure 1: Results of duration of hospitalization of patients in the test and control groups**

## Discussion

This study demonstrates that inhaled 3% HS is an effective treatment for infants hospitalized with viral bronchiolitis. We found that nebulized 3% HS decrease

bronchiolitis severity score after 12 h of treatment and its effect subsided after more than 48 h. Anil et al [50] found similar effect however; this response occured earlier (120 min). In regard to hospital stay; our study showed a decrease in mean of hospital stay length from 42.2 to 36.3 h with a P-value of 0.002. This observation did not go with Kuzik et al. findings [51], may be due to the large population size (639) and younger patient (<7 months old) investigated in Kuzik et al. study. However, the current results were consistent with those obtained by Luo Z, et al. [52, 53].

Previously, five trials (Al-Ansari [54], Anil [50], Grewal [55], Ipek [56] & Mandelberg [57]) did not find a significant difference between the hypertonic saline group and the 0.9% saline group in terms of room air saturation of oxyhaemoglobin throughout the study period. However; we found a significant improvement in oxygen saturation in the early hours of treatment. We did not find any adverse effects to the treatment, and in this regard all authors have stated that the administration of 3% HSS alone [58] or in combination with bronchodilators is harmless, safe, and cheap. Sarrell et al. [59] and Al-Ansari [54] both have conducted their study on outpatient and emergency room setting which is on the case in our study because there is difficulty to fallow our patients in these wards. However; the present results are consistent with the findings of Sarrell et al. [59] and Al-Ansari [54]. Kuzik et al. [51] have conducted their study over a long period of time, during the winter of years 2007-2010, with a large population size. The population size of the current study is small relative to those of Kuzik et al. hence, such point could be considered as a weak point.

In Al-Ansari [54] study, two concentrations of hypertonic saline (3% and 5%) were used. No superiority of 5% saline over 3% saline was observed in improving the clinical score at 24 h and 48 h after randomization. However, further studies are still needed to establish the optimal concentration and treatment regime of nebulized hypertonic saline in infants with viral bronchiolitis. In our study we utilized Wang [49] bronchiolitis severity score. Other researcher have used Respiratory Distress Assessment Instrument (RDAI) which assesses chest retractions and auscultatory findings, and provides a score ranging from 0 to 17, with a higher score indicating more severe respiratory distress [60]. The later score is highly subjective and may exhibits a bias. Al-Ansari [54], Anil [50], Grewal [55] have used the rate of readmission as an outcome. This was not considered in our

study because of limited time of study. However; the pooled results of these trials did not demonstrate significant benefits of nebulized hypertonic saline in reducing the risk of readmission.

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**Table 2:**

A comparison between test & control groups according to bronchiolitis Severity score

| | Group | N | Mean ±SD | P-value |
|---|---|---|---|---|
| Baseline Score | Test | 84 | 4.84±.65 | .152 |
| | Control | 81 | 4.98±.62 | |
| 12 h Score | Test | 84 | 4.02±.86 | .001 |
| | Control | 81 | 4.45±.72 | |
| 24 h Score | Test | 84 | 3.10±.77 | .000 |
| | Control | 81 | 3.66±.75 | |
| 36 h Score | Test | 59 | 2.38±.55 | .000 |
| | Control | 75 | 2.93±.68 | |
| 48 h Score | Test | 18 | 2.22±.42 | .046 |
| | Control | 35 | 2.57±.65 | |
| More than 48 h Score | Test | 4 | 2.00±.81 | .242 |
| | Control | 6 | 2.66±.81 | |

**Table 3:**

A comparison between test and control groups in oxygen saturation

| | Group | N | Mean ±SD | P value |
|---|---|---|---|---|
| Baseline Pao2 | Test | 84 | 95.03±.75 | .000 |
| | Control | 81 | 94.49±1.15 | |
| 12 h Pao2 | Test | 84 | 95.50±.70 | .003 |
| | Control | 81 | 95.08±1.01 | |
| 24 h Pao2 | Test | 84 | 96.33±.92 | .000 |
| | Control | 81 | 95.65±1.21 | |
| 36 h Pao2 | Test | 59 | 96.77±.92 | .000 |
| | Control | 75 | 96.01±1.19 | |
| 48 h Pao2 | Test | 18 | 96.72±.82 | .112 |
| | Control | 35 | 96.20±1.23 | |
| More than 48 h Pao2 | Test | 4 | 97.75±.95 | .055 |
| | Control | 6 | 96.16±1.16 | |

In conclusion, the nebulization with 3% hypertonic saline is safe and may be superior to the current treatment of early infirmary outpatient treatment of bronchiolitis. It is recommended to plan for a multicenter trials to explore the clinical benefit of this therapy with a large sample size.

**Table 4:**

A comparison between test and control group regarding duration of hospital stay

| | Group | N | Mean ±SD | P-value |
|---|---|---|---|---|
| Length of hospital stay (h) | Test | 84 | 36.28±12.14 | 0.002 |
| | Control | 81 | 42.24±11.97 | |

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