

Hypertonic (3%) Saline Vs 0.9% Saline Nebulization for Acute Viral Bronchiolitis: A Randomized Controlled Trial

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Objective: To compare the length of hospital stay (primary) and improvement in clinical severity scores (secondary) among children with bronchiolitis nebulized with 3 % hypertonic saline or 0.9% saline.

Design: Randomized double blind controlled trial.

Setting: Tertiary care teaching hospital.

Patients: Hospitalized children (1-24 months) with acute bronchiolitis of moderate severity.

Intervention: Nebulization of 4 ml of 3% hypertonic saline or 4 mL of 0.9% saline, along with 2.5 mg salbutamol, at 4-hourly intervals till the patient was ready for discharge.

Results: Baseline characteristics were similar in two groups. Median clinical severity score at admission was 6 (IQR-1) in both the groups. Clinical severity scores monitored afterwards 12-hourly till discharge (132 h) did not show statistically significant differences in 3% and 0.9% saline groups. Mean length of hospital stay (time to reach predefined clinical severity score<3) was 63.93 ± 22.43 h in 3% saline group and 63.51 ± 21.27 h in 0.9% saline group ($P=0.878$). No adverse events were reported by the parents, caregivers or treating medical attendants in both groups.

Conclusion: Nebulized 3 % saline is not superior to 0.9% saline in infants with clinically diagnosed acute bronchiolitis.

Keywords: 3% saline nebulization, Bronchiolitis, Management.

Viral bronchiolitis is a common reason for hospitalizations in infants and contributes to huge economic burden [1, 2]. Bronchiolitis is generally seasonal and hospitalization peaks between 3 and 6 months of life [2]. The standard treatment remains supportive care and includes ensuring adequate oxygen exchange, fluid intake and feeding of the infant [3, 4]. Meta analyses of data on the most-used therapies for acute bronchiolitis namely, nebulized bronchodilators, epinephrine, glucocorticoids and chest physiotherapy have failed to prove any effect on relevant clinical outcomes, in comparison with placebo except some benefits of epinephrine compared to placebo for short-term outcomes for outpatients, particularly in the first 24 hours of care [5-8]. Current clinical practice guidelines do not recommend the routine use of any medication but despite the evidence, use of ineffective therapies for bronchiolitis remains high [9].

Recently, several investigators have reported the use of hypertonic saline solution for infants with bronchiolitis with substantial benefits of therapy reported by many of them [10-19]. It has been reported to alter mucociliary clearance favorably in both normal and diseased lungs in multiple clinical settings including bronchiolitis [20-24]. This modality has enormous potential for cost-saving, both in developing and developed countries, more so if it

could actually reduce length of hospitalization as suggested by a recent Cochrane review [13]. Thus, based on the available literature, we hypothesized that 3 % hypertonic saline would shorten length of hospital stay as compared to 0.9% saline in patients with bronchiolitis. We conducted this study to evaluate the efficacy of nebulized 3 % hypertonic saline in children diagnosed with clinical bronchiolitis.

Accompanying Editorial: Pages 733-4

METHOD

We designed a randomized, double-blind, controlled trial involving infants and children aged 1 to 24 months hospitalized with acute bronchiolitis of moderate severity. Children with clinical presentation of viral bronchiolitis and hospitalized with a clinical severity score 3-6 were included [24,25]. Bronchiolitis was defined by first episode of wheezing along with prodrome of upper respiratory tract infection including rhinorrhea, cough, and sometimes low-grade fever, which may progress to dyspnoea. Children with obtunded consciousness, cardiac disease, chronic respiratory disease, previous wheezing episode, progressive respiratory distress requiring respiratory support other than supplemental oxygen were excluded. Those having

received nebulized hypertonic saline within the previous 12 hours were also excluded. The Institutional ethics committee of our hospital approved the study. Signed informed consent was obtained from the parents of all children. All patients were enrolled within 24 hours of admission to the hospital. Computer generated random numbers were used for enrolment in consecutive manner and patients were randomly assigned receive either 4 mL of 3% hypertonic saline or 4 mL of 0.9% saline nebulization along with 2.5 mg salbutamol at intervals of 4 hours, six times daily till the patient was ready for discharge. There was no detectable difference in color, smell, or other physical properties between 0.9% saline solution and 3% hypertonic saline solution. The combination code of the therapeutic package (0.9% saline vs 3% hypertonic saline) was not available to the investigator or treating medical staff. The code was deposited with the statistician. We used a conventional jet nebulizer with tight-fitting face mask connected to a source of pressurized oxygen set to a flow rate of 7 L/min through tight-fitting face mask. The nebulization was continued till the nebulization chamber was empty. Patients were examined by investigators at the study entry and every day. Monitoring parameters for improvement or worsening of the condition were measured and recorded at admission and then at 12 hourly intervals using the clinical score described by Wang, *et al.* [25]. Discharge criteria included feeding well orally, no need for intravenous fluids and supplemental oxygen, clinical severity score ≤ 3 , absence of accessory muscle use or tachypnea (respiratory rate < 31 breaths/min) and oxygen saturation $> 92\%$ on air. We measured length of hospital stay from admission to time taken to reach clinical severity score < 3 .

Statistical analysis: Primary objective of interest was to compare the length of hospital stay (time taken to reach clinical severity score < 3) and secondary objective was to compare the improvement in clinical severity scores in hospitalized children with acute bronchiolitis nebulized with 3% hypertonic saline and normal saline. Reduction in length of hospital stay of 1 day was previously proposed as being clinically significant. It was anticipated that this would require a sample size of 113 patients in each arm. This number was based on a pre study mean length of hospital stay of 3.5 ± 2.9 days [17]. Each variable was scanned for normalcy of distribution. Categorical variable were compared using the Chi-square test. All continuous variables were compared using the paired or unpaired t-test as appropriate. A P value < 0.05 was considered statistically significant. To examine the clinical severity scores at 12-hourly intervals Mann-Whitney non-parametric U test was carried out in each

treatment group separately. For this analysis, P value 0.005 was considered significant due to multiple comparisons.

RESULTS

Study was conducted during September 2009 to December 2010 and 277 potentially eligible candidates patients with a clinical diagnosis of bronchiolitis were admitted of which 248 successfully completed the protocol (**Fig. 1**). The two study groups were similar in baseline characteristics (**Table I**) including age, sex and clinical severity score.

Clinical severity scores monitored 12 hourly till discharge (132 hours) did not show statistically significant differences between the two groups (**Fig. 2**). However, it is to be noted that the median clinical severity score at time 0 would be based on 125 subjects whereas the data at 132 hours would be based on only 2 patients. There was no difference in mean length of hospital stay in 0.9% saline (63.93 ± 22.43 hours) & 3% hypertonic saline (63.51 ± 21.27) groups ($P=0.878$). Percentage of patients remaining in each group at 24 hourly intervals is depicted in **Fig. 3**. No adverse events related to nebulized therapy were reported by the parents, caregivers or treating medical attendants in both groups.

DISCUSSION

Ours is the one of the largest studies comparing 3% hypertonic saline and 0.9% (normal) saline nebulization in hospitalized children with acute bronchiolitis. Both the groups were comparable in baseline characteristics however; we did not find any advantage of hypertonic (3%) saline over normal (0.9%) saline in terms of length

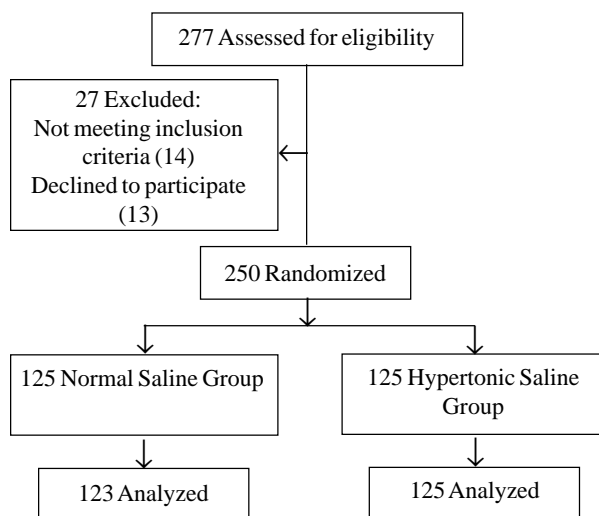


FIG.1 Participant flow diagram.

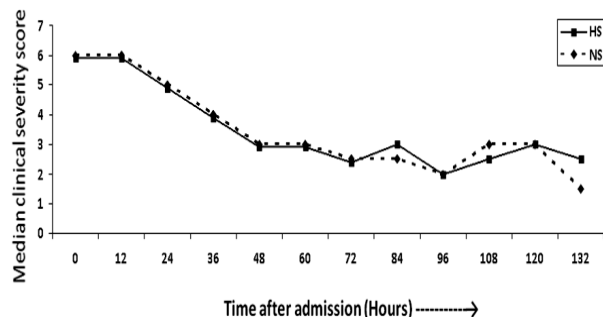


FIG. 2 Median clinical severity score of two groups at 12-hourly intervals.

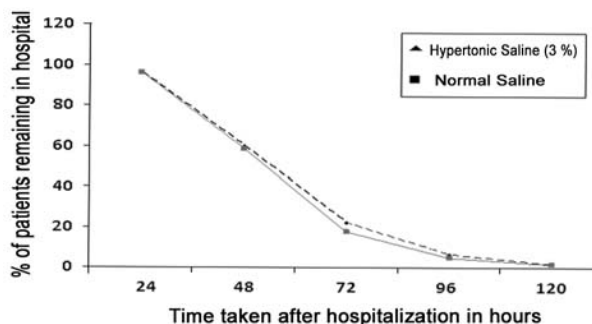


FIG.3 Patients remaining in each group at 24-h intervals.

of hospital stay and clinical severity scores monitored from admission till discharge.

Shorter length of hospital stay and lower admission rates have been reported to be objective and clinically meaningful measure of cost effectiveness [26, 27]. In the Cochrane meta analysis (four studies) 24.1% shorter (mean 1.16 days, 95% CI -1.55 to - 0.77 days) length of hospital stay was reported with hypertonic saline [13]. However, one of these studies reporting the maximum reduction (-1.4 days) with hypertonic saline had longer length of stay (almost double that of other 3 studies) in both the groups leading to heterogeneity of data [17]. Khalid, *et al.* [18] have recently reported shorter length of stay with hypertonic saline but if we look at the actual length of hospital stay among the different groups, there is difference of few hours only which may not be significant clinically. Revisit rate 7 days after discharge was also similar in all the groups in their study reflecting the non superiority of hypertonic saline. Mean length of

hospital stay was similar with 3% and normal saline in our study but it was shorter in both the groups as compared to all other investigators [18].

Most of the studies conducted in emergency care or outpatient settings did not show any significant advantage of hypertonic saline over normal saline in terms of improvement in clinical severity scores or hospitalization rates [11,12,14]. However, studies conducted in hospitalized patients with bronchiolitis have reported better improvement in clinical severity scores with hypertonic saline but the magnitude of improvement differed on different treatment days varying from 15.7 % on day 1 to 29.4 % on day 3 in hypertonic saline group [10,13,15-17]. Concentration dependent improvement (normal saline <3% saline <5% saline) in clinical severity scores reported by Khalid, *et al.* [18] were measured immediate post nebulization but transient improvement may not have effect on length of hospitalization [18]. We did not find any significant difference in CS score at enrollment and thereafter at 12 hourly intervals till discharge in both the groups.

TABLE I BASELINE CHARACTERISTICS OF STUDY SUBJECTS

Characteristics	Hypertonic saline N=125	Normal saline N=123
Age, mo (mean)	4.93 ± 4.31	4.18±4.24
No. of patients in different age groups		
1-6 mo	93	105
7-12 mo	24	13
12-24 mo	8	5
Male/female (n)	97/28	92/31
Duration of symptoms* (d)	3.6±2.87	3.8±2.34
Baseline O ₂ saturation%	94.43±2.77	95.23±2.45
Mean time (h) [#]	8.6±4.63	9.1±7.62
Clinical score [^] (median)	6	6

* at enrollment; [#] admission to enrollment; [^] at admission.

Sood, *et al.* [28] have demonstrated that increasing the volume of airway surface liquid is associated with increased rates of mucociliary clearance in normal subjects. They found that the change in depth of airway surface liquid after normal saline or hypertonic saline inhalations is a function of the mass of NaCl added to the airway surface by the aerosols of different concentrations of NaCl. Ceiling effect of higher inhaled NaCl could be the possible reason for inability to document any difference with hypertonic saline and normal saline in our study.

We did not have a placebo group due to ethical considerations as the only placebo for nebulization therapy could be NS which itself is a treatment modality. We did not attempt virological diagnosis as we did not have the facility. Though this is the actual clinical

What This Study adds?

- Frequent normal saline nebulization is as good as 3% saline nebulization in hospitalized infants with moderate to severe acute bronchiolitis.

scenario for management of bronchiolitis in developing countries yet, considering the age limit we might have enrolled a few children with diagnosis other than bronchiolitis.

To conclude, nebulized 3 % hypertonic saline is not superior to 0.9% saline in infants and children with clinically diagnosed acute bronchiolitis (without RSV confirmation). Further large-scale trials are required to prove its clinical benefits before recommending its routine use in patients with acute viral bronchiolitis.

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