Comparative efficacy of nebulization with 3% hypertonic saline and 0.9% normal saline in the management of acute bronchiolitis

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ABSTRACT

Background: There is a dearth of therapeutic modalities for the management of bronchiolitis in children. **Objective:** The objective of the study was to compare the improvement in clinical severity scores and the length of hospital stay (LOS) among children with bronchiolitis nebulized with either 3% hypertonic saline (HS) or 0.9% normal saline (NS). **Materials and Methods:** A total of 360 hospitalized patients of age 1–24 months, diagnosed as a case of acute bronchiolitis of moderate severity, were randomized to receive either 4 ml of 3% HS (Group A) or 4 ml of 0.9% NS (Group B) along with 1.5 mg of epinephrine in each arm, at 4 hourly intervals till the patients were ready for discharge. Appropriate statistical analysis was carried out using the collected data. **Results:** All the baseline characteristics were similar in both the groups. There was a significant (p=0.0011) reduction of 13 h (12.2%), i.e., from 4 days 23 h in Group B (NS) to 4 days 10 h in Group A in the mean LOS and significant difference (p=0.0001) in the clinical severity score was noted from the 2nd day onward in Group A as compared to Group B. No adverse events were observed or reported by the treating medical team or the patients' caregiver in both the study groups. **Conclusion:** Nebulization with 3% HS is superior to 0.9% NS nebulization in infants with clinically diagnosed acute bronchiolitis.

Key words: *Bronchiolitis, Hypertonic saline, Nebulization, Normal saline*

Bronchiolitis refers to the inflammation of the bronchioles and is defined according to the AAP guidelines as a viral upper respiratory tract infection associated with respiratory distress and wheezing in children younger than 2 years of age [1]. Common viral causes of bronchiolitis include respiratory syncytial virus (RSV), parainfluenza virus, influenza, human metapneumovirus, and rhinovirus of which RSV accounts for approximately 60–75% of bronchiolitis cases [1]. The standard treatment comprises of sufficient humidified oxygen inhalation, fluid intake, and supportive care [2,3]. The review of recent literature has focused on new therapies such as 3% hypertonic saline (HS) for the treatment of bronchiolitis. It modifies mucociliary clearance in both normal and diseased lungs in patients with bronchiolitis [4-8].

The updated AAP guidelines support the use of 3% HS nebulization for infants and children hospitalized for bronchiolitis [1]. A recent Cochrane review suggested that it reduces the length of hospitalization and therefore has an enormous cost-saving potential, both in developing and developed countries [9]. Due to the paucity of therapeutic options for bronchiolitis and possibility of benefit by the usage of 3% HS, this study was conducted to compare the efficacy of 3% HS with 0.9% normal saline (NS) nebulization in the management of acute bronchiolitis.

MATERIALS AND METHODS

This randomized, double-blind, control study was conducted from January 2018 to June 2019 in the pediatric ward of a tertiary care teaching hospital in Jaipur, Rajasthan in acute bronchiolitis patients aged 1–24 months. Bronchiolitis of moderate severity was decided by clinical severity score (CSS) as described by Wang *et al*. [10]. A signed informed consent was obtained from the parents or guardians of the study subjects. 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 dyspnea [11].

The primary outcome was to compare the improvement in CSS in the study subjects and secondary outcome was to compare the length of hospital stay (LOS) (time taken from admission till discharge). It was hypothesized that 3% HS is not superior to 0.9% NS nebulization in hospitalized children with bronchiolitis. Sample size was calculated using the formula: $N=[(z1+z2)^2(O1^2+O2^2)]/(U1-U2)^2$ where N=sample size; z1 = confidence level; Ó1 & Ó2 = standard deviation of outcome variable (CSS) in the 1st (HS) and 2nd (NS) intervention group, respectively; and Û1 & Û2 = mean change in CSS among the 1st (HS) and 2nd (NS) intervention group, respectively. To have an

adequate power of 95% and an error of 5% (α=0.05), z2=1.64 was considered and a sample size of 167 patients in each group was calculated.

The children with cardiac disease, obtunded consciousness, chronic respiratory disease, previous wheezing episode, progressive respiratory distress requiring respiratory support other than supplemental oxygen, those who received nebulized HS within the previous 12 h, and having CSS>6 were excluded from the study. Enrolment of all patients in this study was done within 24 h of admission to the hospital. Computer-generated random numbers were used in consecutive manner and patients were randomly assigned into two groups: Group A (HS; n=172) received 4 ml of 3% HS and Group B (NS; n=179) received 4 ml of 0.9% NS nebulization at an interval of 4 h, 6 times daily till the patients were ready for discharge. Both were used in combination with 1.5 mg epinephrine. There was no detectable difference in color, smell, or other physical properties between them. The combination code of the therapeutic package was not available to the investigator or treating medical staff. The code was deposited with the nurse in charge of the pediatric ward. A conventional jet nebulizer with a tight-fitting face mask connected to a source of pressurized oxygen set to a flow rate of 7 l/min was used. The nebulization continued till the chamber was empty.

Vital parameters including oxygen saturation were simultaneously being monitored using pulse oximeter. All the study subjects were monitored for possible adverse effects such as cough, desaturation, vomiting, diarrhea, tachycardia, hypertension, pallor, and tremor during and after nebulization by 3% HS or NS. Examination of patients was done at admission and every day on a 12 hourly basis and CSS was recorded simultaneously by the examiner to indicate any improvement or worsening of the condition. Discharge criteria were CSS<3, good oral intake, when intravenous fluids and supplemental oxygen was not needed, no use of accessory muscle or tachypnea (respiratory rate <31 breaths/min) and oxygen saturation >92% on air. The LOS was measured from admission to time taken to reach CSS<3.

Each variable was scanned for normalcy of distribution. Categorical variables were compared using the Chi-square test. All continuous variables were compared using the unpaired t-test as appropriate using SPSS-20 software. p<0.05 was considered statistically significant. The study was approved by the Institutional Ethical Committee.

RESULTS

Of the 396 study subjects with bronchiolitis, 360 children were randomized in two Groups-A and B as shown in flowchart (Figure 1). The baseline characteristics included age, sex, and CSS which were similar in both the groups (Table 1).

The mean LOS (Table 2) in Groups A and B was 106.03±18.19 and 119.19±22.08 h, respectively (CI: 2.87–11.46), which

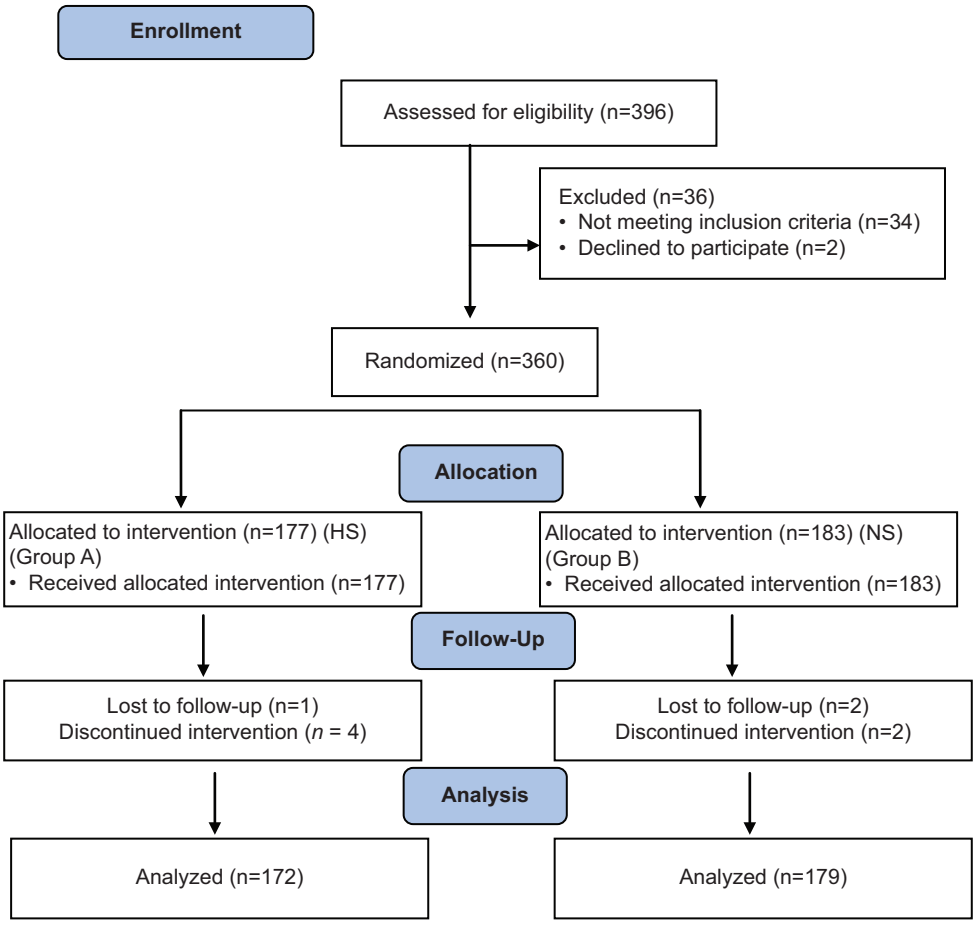

Figure 1: Flowchart

indicates that there was a significant (p=0.0011) reduction of 13 h (12.2%), i.e., from 4 days 23 h in Group B to 4 days 10 h in Group A.

Mean CSS (Table 3) was calculated on different days of admission. There was no significant difference (p=0.5272) on day of admission and the 1st day, but significant difference (p=0.0001) in the CSS was noted from the 2nd day onwards in Group A as compared to Group B. No adverse events during and after nebulization by 3% HS or NS were observed or reported.

DISCUSSION

This study indicates that nebulization with 3% HS in hospitalized infants with bronchiolitis reduces the and improves the CSS significantly as compared to 0.9% NS. Consistent with the findings of the present study, the previous studies [12-14] have reported the use of HS for infants in bronchiolitis with substantial benefits of therapy. Mandelberg *et al*. have observed that nebulized HS decreases the LOS as compared with NS among infants hospitalized with the disease [12]. In the present study, the 6 times daily dose and subsequent duration of effect proved to be sufficient to shorten hospital stay significantly. This observation is in concordance with Guidice *et al*. [14].

Wang *et al*. performed a meta-analysis and concluded that infants treated with 3% HS in combination with additional medication exhibited a shorter duration of hospitalization, a lower CSS score, and decreased readmission rates compared with NS [15]. Previously, Sarrell *et al*. had shown that substituting HS for NS (2 ml) in the inhalation mixture for delivering bronchodilator improved CSS and decreased hospitalization rates in ambulatory children [16]. Zhang *et al*. [17] and Kuzik *et al*. [18] used bronchiolitis severity score to evaluate patients overtime and they found that inhaled 3% HS with epinephrine administered by nebulization every 6–8 h improved the score and reduced LOS in hospitalized patients when compared with 0.9% NS with epinephrine. No adverse effects were reported in any of these studies. These findings are in consonance with the present study as in this study, the mean LOS was much shorter (13 h shorter) in the HS group than that in the NS group.

However, Grewal *et al*. suggested that immediate clinical benefits may not be seen with nebulized HS [19]. They also found a difference in hospitalization rate that was significant clinically, but not statistically significant due to their limited sample size. Sharma *et al*. observed that the CSS in 3% HS and 0.9% NS groups was not significantly different. Therefore, nebulized 3% HS was not superior to 0.9% saline in infants diagnosed with bronchiolitis [11].

Airway edema and mucus plugging are the predominant pathological features in acute bronchiolitis. HS decreases airway edema, improves mucus rheological properties and mucociliary clearance, and thus decreases airway obstruction [20]. It facilitates removal of inspissated mucus through osmotic hydration, disruption of mucus strand cross linking, and reduction of mucosal edema [21,22]. HS inhalation can cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway function in infants with bronchiolitis. A relatively low concentration (3%) was used to decrease the possible negative effect of higher concentrations (7%) on the ciliary beat frequency and to decrease risk of bronchospasm [23]. It was always administered in conjunction with epinephrine solution to avoid any possible bronchoconstriction effect.

In this study, no such detrimental effect was seen which is in concordance with the excellent safety profile reported by others [24-28]. However, Everard *et al.* noted adverse effects which included self-resolving bradycardia, desaturation, cough, tachypnea, and chest infection which resolved after 6 days [29]. Similarly, Flores *et al.* reported that exacerbation of coughing and excessive rhinorrhea was common in 3% HS group than in 0.9% NS group. They also observed apnea, cyanosis, saturation dips, tachycardia, and vomiting [30]. Kose *et al*. observed no adverse effects with the use of 0.9% NS or 3% HS, but bronchospasm in two infants and cough in another two infants were reported by them after nebulization with 7% HS [31].

Table 1: Baseline characteristics of the study subjects

Characteristics	Group A (HS)	Group B (NS)	p
Age (in months)	9.4±4.31	8.5±4.24	0.5341
Number of patients in different age groups			
1–6 months	89	98	
7–12 months	47	43	
12–24 months	36	38	
Male/female (n)	99/73	109/70	
Duration of symptoms (d)	2.61±2.84	2.56±2.7	0.4362
Baseline O_2 saturation%	93.33±1.25	93.19±1.41	0.3331
Baseline clinical score (mean)	5.34±0.73	5.29±0.75	0.5272

Table 2: Changes during hospital stay

Characteristics	HS (n=172)	NS (n=179)	p-value	95% confidence interval
Respiratory rate, breaths/min				
Admission	51.45±4.52	51.25±4.76	0.6838	–0.77 to 1.18
Discharge	30.02±2.78	30.44±2.62	0.1416	–0.99 to.14
Oxygen saturation%				
Admission	93.19±1.41	93.33±1.25	0.3331	–0.42 to 0.14
Discharge	98.66±1.09	98.46±0.96	0.0727	–0.02 to 0.41
Length of stay (hours)	106.03±18.19	119.19±22.08	0.0011	2.87 to 11.46

Table 3: Mean clinical severity score

CSS	HS (n=172)	NS (n=179)	p-value	95% confidence interval
0 day	5.34±0.73	5.29±0.75	0.5272	–0.21–0.11
1st day	4.77±0.86	4.90±0.89	0.1843	–0.06–0.31
2nd day	3.506±0.767	4.024±1.020	0.0001	0.327–0.709
3rd day	2.39±0.84	2.78±1.14	0.0003	0.18–0.61
4th day	1.25±0.96	1.72±1.16	0.0002	0.23–0.71
5th day	0.56±0.75	0.94±0.86	0.0034	0.13–0.64

The strength of this study was that it was adequately powered due to its sufficient sample size. Further, it had a double-blinded design which minimized the common bias and limitations associated with research. The limitations of this study were that there was no placebo group due to ethical considerations as the only placebo for nebulization therapy could be NS which itself is a treatment modality. Virological diagnosis was not attempted due to resource constraints. Since this study only consisted of mild-to-moderate patients with bronchiolitis, results may need caution while extrapolating them to infants with severe disease.

CONCLUSION

It is of supreme importance for pediatricians to be aware of the efficient and safe treatment for bronchiolitis. This study establishes that HS nebulization is an efficient, simple, safe, and economical treatment modality in bronchiolitis. However, further studies involving a larger sample size are required to support this therapeutic intervention.

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