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RESEARCH ARTICLE

HYPERTONIC (3%) SALINE VS 0.9% SALINE NEBULIZATION FOR ACUTE VIRAL BRONCHIOLITIS: A RANDOMIZED CONTROLLED TRIAL AT A TERTIARY CENTRE IN CHENNAI

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ABSTRACT

Introduction: Lower respiratory tract infections are a common cause of hospitalisation in infants. It is estimated that infants younger than 12 months with bronchiolitis account for 18% of all paediatric admission , representing a great burden to industrialised healthcare systems each winter. Bronchiolitis is defined as the first respiratory tract infection in infants younger than 12 months. Clinically, it can be manifested by cough, tachypnoea, apnoea, increased respiratory effort, fever, nasal congestion and rhinorrhoea. On chest auscultation, the key feature is diffuse bilateral inspiratory crackles. The most common virus detected in children with bronchiolitis is respiratory syncytial virus (RSV). **Aim of the Study:** 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. **Materials and Methods:** It is a randomized, double-blind, controlled trial involving infants and children aged 1 to 24 months hospitalized with acute bronchiolitis of moderate severity. 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 was done till the patient was ready for discharge. Monitoring parameters for improvement or worsening of the condition were measured and recorded at admission and then at 12 hourly intervals. **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 63.91 ± 22.46 h in 3% saline group and 63.54 ± 21.25 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.

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INTRODUCTION

Viral bronchiolitis is a common reason for hospitalizations in infants and contributes to huge economic burden (Yorita *et al*., 2008; Deshpande, 2003). Bronchiolitis is generally seasonal and hospitalization peaks between 3 and 6 months of life (Deshpande, 2003). The standard treatment remains supportive care and includes ensuring adequate oxygen exchange, fluid intake and feeding of the infant (Zorc, 2010; Subcommittee on Diagnosis and Management of Bronchiolitis, 2006). 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 (Gadomski, 2006; Hartling, 2011; Patel, 2004; Perrotta, 2006). 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 (Landrigan, 2008). 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 (Mandelberg, 2003; Grewal *et al*., 2009; Anil, 2010; Zhang, 2008; Sarrell, 2002; Tal, 2006; Kuzik *et al*., 2007; Luo, 2010; Khalid, 2010; Luo, 2011). It has been reported to alter mucociliary clearance favorably in both normal and diseased lungs in multiple clinical settings including bronchiolitis (Daviskas 1996; Wark, 2007; Kellett, 2005; Shoseyov, 1998). This modality has enormous potential for cost-saving, both in

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developing and developed countries, more so if it could actually reduce length of hospitalization as suggested by a recent Cochrane review (Zhang *et al*., 2008). 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.

MATERIALS AND 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 (Shoseyov, 1998; Wang, 1992). 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 otherthan 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.* (2010). 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 score <3.

RESULTS

Study was conducted during September 2018 to September 2019 and 123 potentially eligible candidates patients with a clinical diagnosis of bronchiolitis were admitted of which only 112 candidates met the inclusion criteria. The two study groups were similar in baseline characteristics (Table 1) including age, sex and clinical severity score.

Table 1. Baseline characteristics of study subjects

Characteristics	Hypertonic Saline N=56	Normal Saline N= 56
Age, mo(mean)	4.89± 4.34	4.15±4.25
No. of patients in different age group		
1-6mo	40	48
7-12 mo	12	5
12-24 mo	4	3
Male/Female(n)	43/13	41/15
Duration of symptoms(d)	3.5±2.77	3.7±2.31
Baseline O_2 saturation%	94.33±2.71	95.10±2.45
Mean time (h)#	8.6±4.63	9.2±7.62
Clinical score^ (median)	6	6

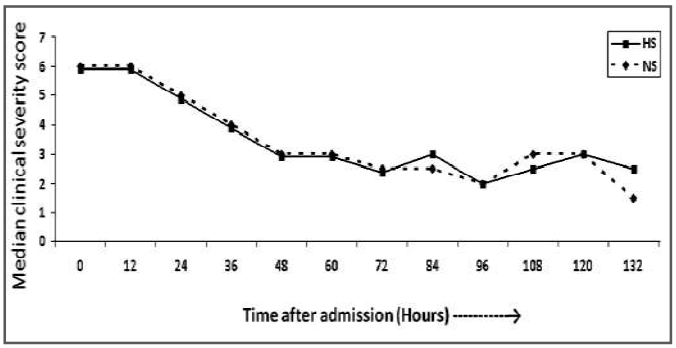

Fig. 2 Median clinical severity score of two groups at 12-hourly intervals

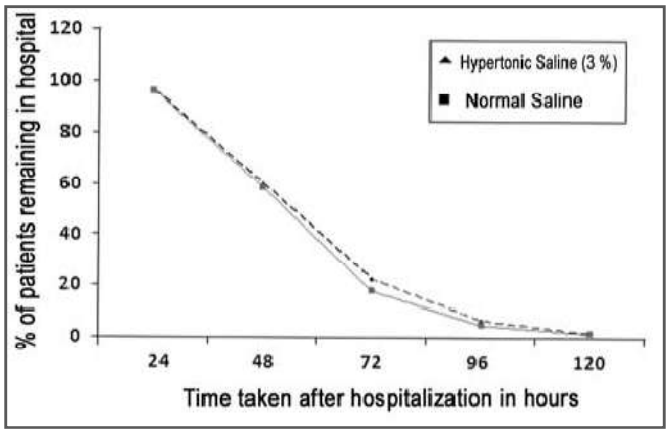

Fig. 3. Patients remaining in each group at 24-h intervals

Clinical severity scores monitored 12 hourly till discharge (132 hours) did not show statistically significant differences between the two groups (Fig. 1). There was no difference in mean length of hospital stay in 0.9% saline (63.91 ± 22.46 hours) & 3% hypertonic saline (63.54 ± 21.25) groups (*P*=0.878). Percentage of patients remaining in each group at 24 hourly intervals is depicted in Fig. 2. 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 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 (Ralston, 2016; Horner *et al*.,

2010). 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 (Luo, 2010). Khalid, *et al.* (2010) 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 (Khalid *et al*., 2010). 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 (Grewal, 2009; Anil, 2010; Sarrell, 2012). 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 (Mandelberg *et al*., 2003; Tal, 2006; Kuzik, 2007; Luo, 2010). Concentration dependent improvement (normal saline <3% saline <5% saline) in clinical severity scores reported by Khalid, *et al.* (2010) were measured immediate post nebulization but transient improvement may not have effect on length of hospitalization (Khalid *et al*., 2010).

We did not find any significant difference in CS score at enrollment and thereafter at 12 hourly intervals till discharge in both the groups. Sood, *et al.* (2003) 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 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.

Conclusion

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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