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Original Article

Paediatrics Section

Comparative Study of 3% Hypertonic Saline Nebulisation Versus 0.9% Normal Saline Nebulisation for Treating Acute Bronchiolitis

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ABSTRACT

Introduction: Bronchiolitis is commonly noticed condition in children, especially in infants and characterised by inflammation of bronchioles. Inspite of this common occurrence the evidence for the treatment options is limited.

Aim: To compare the effect of 3% Hypertonic Saline (HS) nebulisation with 0.9% Normal Saline (NS) nebulisation for treating acute bronchiolitis in moderately ill hospitalised infants and children (<18 months) on Length Of Hospital Stay (LOS) and improvement in clinical severity score.

Materials and Methods: This is a randomised controlled trial, done in a tertiary care paediatric hospital over a period of one year from April 2014 to March 2015. Out of 189 children randomised, 96 patients and 93 patients received HS nebulisation and NS nebulisation respectively. Treating doctors and patients were blinded to intervention and outcome.

Results: Reduction in clinical severity score in 3% HS nebulisation group was 2.26 (0.684) and in 0.9% NS nebulisation group was 1.23 (0.492), with statistically significant p<0.001. LOS in 3% HS nebulisation group was 1.45 (0.540) days and in 0.9% NS nebulisation group was 2.35 (0.619) days with mean difference of 0.91 (0.084) day with statistically significant p<0.001.

Conclusion: This study demonstrates that 3% HS nebulisation is safe and effective treatment for infants up to the age of 18 months hospitalised with acute bronchiolitis and decreases hospital stay by about one day.

Keywords: Bronchiolitis, Nebulisation, Respiratory tract infection

INTRODUCTION

Bronchiolitis is defined as first episode of expiratory wheeze of acute onset in a child less than two years of age who has signs of viral respiratory illness like coryza, otitis media, or fever with or without indication of respiratory distress, with chest X-ray showing marked generalised emphysema, patchy consolidation, atelectasis and abnormal linear shadows, due to thickening of the bronchioles [1].

Bronchiolitis is characterised by airway plugging with sloughed epithelium, mucus, and oedema rather than bronchospasm, nevertheless the use of nebulised bronchodilators continue to be common, despite extensive evidences supported by three meta analysis that the benefits are limited, short term, and do not justify routine use [2,3].

Antiviral agents (ribavirin) are used only in special group of children who are at risk of severe disease (chronic lung disease, congenital heart disease, etc.,). There is no role for antibiotics, but are considered whenever secondary bacterial pneumonia is suspected or documented [4].

Similarly; although, steroids might 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 or ineffective [5].

The treatment options therefore, remains mainly supportive measures including fluids and supplemental oxygen administration, observation and mechanical ventilator support.

Recently, few western studies have shown that nebulisation with 3% HS is more effective than nebulisation with NS in terms of reduction in duration of symptoms and LOS [6]. Though, the exact mechanism is largely unknown it is thought to act by facilitating the removal of inspissated mucus through osmotic hydration, disruption of mucus strand cross linking, and reduction of mucosal oedema [7].

The new observations appear to be effective and promising. The literature review resulted in only one study from our country [8]. Due to very high disease burden in our setting, we had decided to do a randomised controlled trial to compare the effectiveness of 3% HS nebulisation versus 0.9% NS nebulisation for treating acute bronchiolitis in moderately ill hospitalised infants and children (<18 months) on LOS and improvement in clinical severity score.

MATERIALS AND METHODS

Study Design

Randomised, prospective, double blind controlled trial, was conducted at tertiary care teaching hospital over a period of one year, from April 2014 to March 2015.

Inclusion Criteria

Previously healthy infants and children of two months to 18 months of age, getting admitted with first episode of respiratory tract infection with wheeze, starting as a viral upper respiratory infection (coryza, cough, or fever), and a clinical score between 4 and 8 were included in the study [9] [Table/Fig-1].

Variable	0	1	2	3
Respiratory rate, breaths/min	<1yr <50 >1yr <30	51-60 31-45	61-70 46-60	>70 >60
Wheeze	None	Terminal expiratory or audible only with stethoscope	Entire expiration or audible without stethoscope	Inspiration and expiration and audible without stethoscope
Retraction	None	Intercostal only	Tracheosternal	Severe with nasal flaring
General condition	Normal			Irritable, lethargic with poor feeding.

[Table/Fig-1]: Clinical severity score.
A clinical score of less than 4 is considered as mild disease, a score between 4 and 8 as moderate disease and any score more than 8 as severe disease

Exclusion criteria

Includes a history of any of the following: previous episode of wheezing, chronic cardiopul monary disease or immunodeficiency; critical illness at presentation requiring admission to intensive care; the use of nebulised HS within the previous 12 hours; or premature birth (gestational age 34 weeks).

Method

The eligible patients were assessed within 12 hours of admission to hospital for entry into the study. If inclusion/exclusion criteria were satisfied, then informed consent was obtained from at least one parent, and the patient were randomised using a computer generated number sequence into two groups to receive treatment with 4 mL of nebulised study solution containing either 3% HS (study group) or 0.9% NS (control group).

The study was approved by the ethics and scientific committees of the hospital.

The study solution was administered in a double blind fashion: Every two hourly for three doses, followed by every four hourly for six doses, followed by every six hourly until discharge. Study solutions was prepared to have identical appearance. The identity of study solutions was blinded to all participants, care providers, and investigators.

Patients were examined at the enrolment and every day thereafter. Relevant demographic and clinical data was obtained from each patient, which would include the following parameters in particular: age, sex, duration of each symptoms, history of previous wheezing episode/cardiac disease/foreign body aspiration, gestational age, and mode of delivery. Vital parameters (heart rate, respiratory rate, saturation) were measured and recorded. Patients were examined for presence of cyanosis, pallor, and chest retractions. In systemic examination, emphasis was laid on breath sounds and presence of rhonchi or rhonchi with crepitation. A complete blood count and chest X-ray was done for all patients. A clinical score was assigned using a clinical severity score described by Wang EE et al., [9]. The scoring was done daily during the hospital stay and was tabulated. Children showing worsening of clinical scores and general condition during the course of the stay were excluded from the study and treated as the condition necessitates. However, these patients were included in the final analysis and were counted as treatment failures. The duration of hospital stay, was measured using a method previously validated by the Paediatric Investigators Collaborative Network on Infections in Canada studies of hospitalised children with RSV infection (PICNIC study) [10].

Daily assessment was done for every child for continuation of hospitalisation and the reasons for continuation of hospitalisation were categorised into one of the following:

1. Children receiving drug treatment for bronchiolitis (or);

2. Children receiving oxygen supplementation or parenteral fluids because of bronchiolitis (or);

3. Children hospitalised because of underlying (pre-existing) illnessonly; or

4. Children awaiting transport home or uncertain home environment.

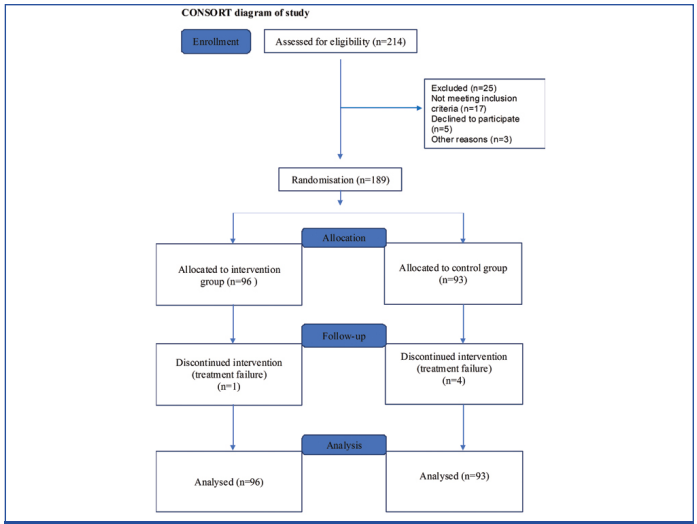
Only those days on which the reason for hospitalisation was one or more of receiving: (1) medications for bronchiolitis; (2) oxygen supplementation or parenteral fluids because of bronchiolitis was recorded as true hospital days. These patients were discharged once they were off oxygen support, maintaining saturations without any respiratory distress and accepting feeds well.

STATASTICAL ANALYSIS

A reduction in LOS of one day has been proposed as being clinically significant and was adopted in this study [11]. With an average hospital stay of 5.0±2.45 days, it was anticipated that this would require a sample size of approximately 95 patients per trial arm, for 80% power, to show a p-value <0.05. Statistical testing was conducted with the Statistical Package for Social Science System version (SPSS 17.0). Continuous variables are presented as mean (SD), and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using student's t-test. Nominal categorical data between the groups were compared using chi square test or fisher's exact test as appropriate. A p-value of <0.05 was considered to be statistically significant.

RESULTS

A total of 189 previously well infants with viral bronchiolitis were enrolled from April 2014 to March 2015. 96 infants were randomised to the HS treatment group, and 93 were randomised to the NS control group. Five infants (one from the HS group and four from the NS group) were withdrawn before study completion but were included in the final intention to treat analysis [Table/Fig-2].



[Table/Fig-2]: CONSORT diagram.

The demographic and clinical features [Table/Fig-3] and radiological features [Table/Fig-4] at the time of hospitalisation were comparable between two groups and were not statistically significant.

Variable	3% HS group	0.9% NS group	p-value
Male sex (%)	62 (64.6%)	65 (69.9%)	0.437
Age in months	4.0 (2.63-8.0)	4.0 (2.0-7.0)	0.519
Family history of asthma	3 (3.1)	1 (1.1)	0.62
Fever$	2.82 (0.71)	2.74±0.77	0.452
Cough$	2.54±0.61	2.58±0.68	0.680
Noisy breathing$	1.63±0.60	1.57±0.56	0.516
Cold$	2.93±0.73	3.05±0.60	0.193
Fast breathing$	1.29±0.457	1.23±0.420	0.304
RR‡	66 (2.71)	67 (2.46)	0.86
SPO_2^	94 (0.86)	95 (0.82)	0.072
Hb (g/dL)	11.94 (1.07)	12.16 (1.10)	0.161
TLC (per mm^3)	7751.76 (1715.40)	7545.68 (1604.94)	0.395

[Table/Fig-3]: Demographic and clinical features at the time of hospitalisation.
Chi square test and student t-test were applied for proportions and means with standard deviation respectively
p-value <0.05 is taken as significant
Median (IQR); $ Mean days (SD); ‡ Breaths/minute (SD); ^ Mean %

The mean LOS in 3% HS group was 1.45 (0.540) days and in NS group was 2.35 (0.619) days [Table/Fig-5]. With mean difference of 0.91 (0.084) day with statistically significant p<0.001 favouring 3% HS group.

CXR$	3% HS group	0.9% NS group	p-value
	Frequency, n (%)	Frequency, n (%)	
HI*	73 (76.0%)	61 (65.6%)	0.114
NAD#	23 (24.0%)	32 (34.4%)	
Total	96 (100%)	93 (100%)	

[Table/Fig-4]: Comparison of CXR between 3% HS group and NS group.
Chi square test was applied for proportions
p-value <0.05 is taken as significant
$ Chest x ray; * Hyperinflation and patchy atelectasis; # No abnormality detected

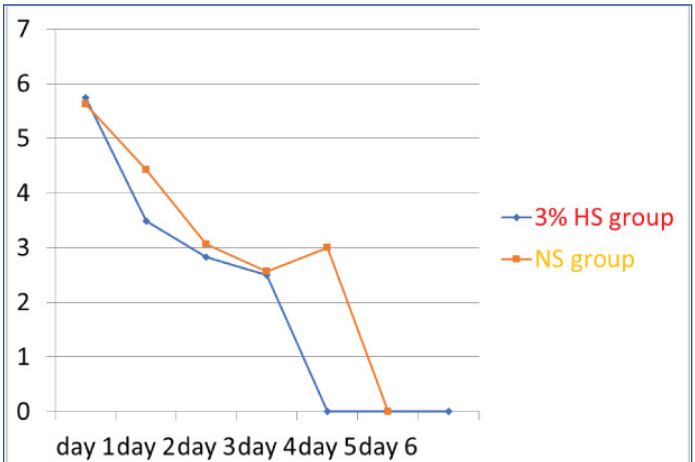
LOS* (Day)	3% HS group	0.9% NS group	p-value
	Frequency, n (%)	Frequency, n (%)	
1	55 (57.3%)	4 (4.3%)	<0.0001
2	39 (40.6%)	55 (59.1%)	0.011
3	2 (2.1%)	31(33.3%)	<0.0001
4	0 (0.0%)	3 (3.2%)	0.117
Total	96 (100%)	93 (100%)	
Mean (SD)	1.45 (0.540)	2.35 (0.619%)	<0.001

[Table/Fig-5]: Comparison of LOS between 3% HS group and NS group.
Chi square test and student t-test were applied for proportions and means with standard deviation respectively
p-value <0.05 is taken as significant
* Length of hospital stay in days; SD: Standard deviation

In the present study, mean reduction in clinical severity score in 3% HS nebulisation group was 2.26 (0.684) and in 0.9% NS nebulisation group was 1.23 (0.492), with statistically significant p<0.001 favouring 3% HS group [Table/Fig-6,7].

RIS*	3% HS group	0.9% NS group	p-value
	Frequency, n (%)	Frequency, n (%)	
0	0 (0.0%)	3 (3.2%)	0.117
1	10 (10.4%)	66 (71.0%)	<0.0001
2	54 (56.3%)	24 (25.8%)	<0.0001
3	29 (30.2%)	0 (0.0%)	<0.0001
4	3 (3.1%)	0 (0.0%)	0.246
Total	96 (100%)	93 (100%)	
Mean (SD)	2.26 (0.684)	1.23 (0.492)	<0.001

[Table/Fig-6]: Comparison of RIS between 3% HS group and NS group.
Chi square test and student t-test were applied for proportions and means with standard deviation respectively
p-value <0.05 is taken as significant
* Reduction in clinical severity score



[Table/Fig-7]: Line diagram showing trend of clinical severity score during hospitalisation between two groups.
Hospitalisation days: X-axis
Clinical severity score: Y-axis

DISCUSSION

Acute bronchiolitis is the most frequent lower respiratory tract infection in infants [12]. Most cases are viral in origin, with the leading cause being Respiratory Syncytial Virus (RVS) other less common pathogens include para influenza viruses, adenovirus, influenza A and B, rhinovirus, human metapneumovirus and mycoplasma pneumonia [13].

Given that virtually all children become infected with RSV by age two years and that at least 1% of these children will develop bronchiolitis Sufficient to require hospitalisation [14], the burden of this disease is high accounting for up to 17% of all infant hospitalisation, at an annual cost of more than $500 million in United States alone [15]. It has been estimated that six lac infants and young children die from RSV annually [1].

Despite the high prevalence and morbidity of bronchiolitis, therapy remains controversial and without widely accepted therapeutic guidelines other than supportive care [16].

In the present study, LOS in HS group was decreased by about one day as compared to NS group. This decrease in hospital stay was also shown in the others studies [6,17-21].

In the present study, we found that clinical severity score was decreased significantly in HS group as compared to NS group. A significant difference in clinical severity score between the treatment and control groups was observed in studies including both inpatients [6,17,19-21] and outpatients [22].

Cochrane systematic review comparing HS with NS also concluded that HS reduces the hospital stay and improves clinical severity score in patients with acute bronchiolitis but the quality of the evidence was low to moderate [23].

There were no adverse events noted in either of the groups in the present study. This was consistent with the earlier studies were in 3% HS was found to be safe in children with acute bronchiolitis [16-18].

Recent study from India by Sharma BS et al., found no difference between 3% HS and NS nebulisation in children with acute bronchiolitis both in decreasing the LOS and clinical severity score [8]. In the present study, we found 3% HS to be superior to NS. This difference can be attributed to age group of study population, smaller babies are included in present study.

Based on the present study results, we recommend 3% HS nebulisation instead of NS nebulisation in patients with acute bronchiolitis as it decreases both duration of hospitalisation and clinical severity score there by reducing hospital burden and cost. There is a need for further studies with large sample size to recommend 3% HS over NS in children with acute bronchiolitis.

LIMITATION

Limitations of the study include small sample size and it was a single centre study. Stringent study design with both treating physician and patients being blinded to both intervention and outcomes were strengths of this study.

CONCLUSION

This study demonstrates that 3% HS nebulisation is safe and effective treatment for infants and children up to the age of 18 months hospitalised with acute bronchiolitis.

The routine use of 3% HS nebulisation in infants hospitalised with acute bronchiolitis will not only return infants to home and their parents to work a day sooner but also will substantially reduce hospital burden and cost.

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