

Comparative Efficacy of Nebulized 3% Hypertonic Saline versus 0.9% Normal Saline in Children with Acute Bronchiolitis

KHANDAKER TAREQUL ISLAM¹, ABID HOSSAN MOLLAH², ABDUL MATIN³, MAHMUDA BEGUM⁴

Abstract

Background: Acute bronchiolitis is leading cause of hospitalization in infants below 2 years of age. Bronchiolitis being a viral disease, there is no effective treatment. 3% nebulized hypertonic saline and 0.9% nebulized normal saline are often used, although there is disagreement over their efficacy. The aim of this study was to evaluate the efficacy of 3% hypertonic saline in children with acute bronchiolitis in reducing clinical severity and length of hospital stay.

Methodology: A randomized control trial carried out in the Department of Pediatrics, Dhaka Medical College Hospital from January 2013 to December 2013. Ninety children from 1 month to 2 years of age hospitalized with clinical bronchiolitis were randomized to receive 3% nebulized hypertonic saline (Group-I) or 0.9% nebulized normal saline (Group-II). Nebulization was done 8 hourly until discharge. Outcome variable were clinical severity score, duration of oxygen therapy and length of hospital stay.

Results: Baseline clinical severity score and O₂ saturation were in group-I 9.0 ± 1.0 and 94.9 ± 1.7 and in group-II 9.3 ± 1.8 and 94.6 ± 2.6 respectively ($p > 0.05$). At 72 hours, the mean severity score for the group-I was 1.64 ± 0.99 and that for the group-II was 3.0 ± 1.48 (95% CI -2.17 to -0.53, $p = 0.002$). The cases of group-I required a shorter duration of oxygen therapy compared to those of group-II (15.0 ± 6.0 hours vs 26.4 ± 5.37 hours, 95% CI -20.35 to -2.44, $p < 0.05$). Forty two (93.3%) of the group-I children recovered by the end of 72 hours and discharged whereas 26 (57.8%) of the group-II children recovered during the same period ($p < 0.05$). Length of hospital stay was shorter in group-I compared to group-II (58.1 ± 22.0 hours vs 74.7 ± 27.2 hours, 95% CI -26.89 to 6.17, $p = 0.002$). None of the cases encountered any side-effects.

Conclusion: Nebulization with 3% hypertonic saline significantly reduced clinical severity, length of hospital stay and duration of oxygen therapy in case of acute bronchiolitis in comparison to 0.9% normal saline and was safe.

Key words: Bronchiolitis, Nebulized 3% hypertonic saline, 0.9% normal saline.

Introduction

Bronchiolitis is an acute inflammatory lesion of the lower respiratory tract. More than 70% cases are caused by respiratory syncytial virus (RSV); other less common pathogens include parainfluenza, influenza, rhinovirus, adenovirus, human metapneumovirus, human bocavirus and mycoplasma pneumoniae^{1,2}. Children become infected with RSV by age 2 years

with peak incidence being in 2-6 months³⁻⁵. Only 1% of these children require hospitalization⁶. In a recent study in different hospitals of Dhaka city, 348 cases were diagnosed as bronchiolitis and were found positive for RSV antibody in 50% these cases⁷.

Bronchiolitis is an infection of the bronchiolar epithelium, characterized by necrosis and sloughing of epithelial cells, oedema, increased secretion of mucus, and peribronchiolar mononuclear infiltration – changes that obstruct flow in the large and small airways, leading to hyperinflation, atelectasis and wheezing^{6,8}.

Despite 4 decades of efforts to deal with the problem, there is no evidence-based clinically effective treatment of bronchiolitis⁶. The standard treatment

1. Junior Consultant, Department of Pediatrics, Shaheed Suhrawardy Medical College Hospital, Dhaka

2. Professor, Department of pediatrics, BIRDEM, Dhaka.

3. Professor, Department of pediatrics, Dhaka Medical College.

4. Junior Consultant, Upazilla Health Complex, Keranigonj, Dhaka

Correspondence: Dr. Khandaker Tarequl Islam, Junior Consultant, Department of Pediatrics, Shaheed Suhrawardy Medical College Hospital, Dhaka. E- mail- khandakeri40@yahoo.com

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for acute bronchiolitis remains supportive care like ensuring sufficient oxygenation and maintaining adequate hydration and nutrition⁸. Bronchodilators like salbutamol, adrenaline, anti-cholinergic drugs- ipratropium bromide and saline nebulization have been used with varying results. There is lack of sufficient evidence for almost all the interventions that are usually tried, including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactant and chest physiotherapy. None of the treatment modalities is specific. Antiviral agents are available, but their use in most patients is controversial. Most of the studies using glucocorticoids in the treatment of bronchiolitis denied a positive therapeutic effect^{8, 9, 10}. The use of β_2 - agonists occasionally resulted in a short-term improvement in patients with bronchiolitis, especially when using epinephrine, 11-14 while others failed to show a significant effect^{8, 15}. Kabir et al in a study showed that antibiotics are used in almost all cases (99%) of bronchiolitis⁷, but the fact is that the antibiotics are of no benefit in the treatment of the condition¹⁶.

Several studies suggested the use of nebulized 3% saline solution for infants with bronchiolitis, due to its ability to lower the viscosity of secretions, reduce airway oedema, and improve mucociliary function. Evidence suggests that hypertonic saline solution favorably alters mucociliary clearance in both normal and diseased lungs¹⁷⁻¹⁹.

To date, there have been 4 trials investigating the use of nebulized 3% hypertonic saline solution in infants with viral bronchiolitis. In 2 of the studies, the improvement in the clinical severity scores was significant in the group treated with hypertonic saline^{20, 21}. In other two studies, the hypertonic saline group had a clinically significant reduction in length of hospital stay^{22, 23}.

A recent Cochrane Database Systemic Review 4 non-emergency based trials (n = 254) examined the role of hypertonic saline in acute bronchiolitis. The authors concluded that nebulized 3% hypertonic saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis²⁴. The only significant adverse effect of nebulized hypertonic saline solution is the risk of bronchospasm as was only established in the asthma²⁵. There is a fairly clear dose-response relationship for hypertonic saline solution and

bronchospasm in individuals with asthma²⁶. Required range to induce bronchospasm is from 4.5-7% saline²⁷. Vast majority of patients with bronchiolitis do not have asthma and the pathophysiologic features of typical bronchiolitis do not involve bronchial smooth muscle hyperresponsiveness. So concern regarding bronchospasm resulting from the use of 3% saline solution among patients with bronchiolitis remains theoretical. No evidence has established that 3% saline solution induces bronchospasm in infants with bronchiolitis²³.

The common practice is to treat hospitalized babies with acute bronchiolitis with inhalation of salbutamol diluted in normal saline solution. The present study hypothesized that simply inhalation of hypertonic saline solution without salbutamol in the form of inhalation by the babies with bronchiolitis may improve their clinical severity scores thereby shortening the length hospitalization.

Materials and methods

The study was a randomized controlled trial conducted in the department of Pediatric, Dhaka Medical College Hospital (DMCH) from January 2013 to December 2013. Children aged between one month to two years presenting with preceding or existing runny nose, cough, breathing difficulty, chest in drawing and rhonch on auscultation admitted during the study period and fulfilled the predefined enrollment criteria was enrolled consecutively as study population. This study included 90 patients with acute bronchiolitis. The two groups were randomly assigned to 3% hypertonic saline nebulization (n=45) and 0.9% normal saline nebulization (n=45). Randomization was done by lottery method, i.e. the parents/ caregiver was given a chance to pick up sealed encoded envelope from a box of eight envelope; Of them 4 containing the name of 3% hypertonic saline and other 4 containing the name of 0.9% normal saline. If the envelope contains 3% nebulized hypertonic saline the child was assigned to Group-I, and if the envelope contains 0.9% nebulized normal saline was assigned to Group-II. In this way the required numbers of children were randomly distributed between Group-I and Group-II to receive treatment with 3% nebulized hypertonic saline and 0.9% nebulized normal saline respectively. Relevant history and physical examination findings were recorded in a pre-tested, semi-structured questionnaire. Variables like clinical severity score assessed by using respiratory distress assessment instrument described by Wang et al²⁸, oxygen saturation in room air were measured and recorded

Respiratory distress assessment instrument 28

Variables	0	1	2	3	Total
Respiratory rate	<30 breaths/min	31 to 45 Breaths/min	46 to 60 Breaths/min	>60 breaths/min	3
Wheezing	none	Terminal expiratory or only with stethoscope	Entire expiration or Audible on Expiration without stethoscope	Inspiration and expiration without stethoscope	3
Retraction	none	Intercostals only	Tracheosternal	Severe with nasal flaring.	3
General condition	normal			Irritable, lethargic, or poor feeding	3

on admission as baseline characteristics. Oxygen saturation was measured by using noninvasive pulse oxymeter. A child with oxygen saturation value < 90% was designated as having significant hypoxia. After taking written informed consent drug was given according to dose schedule. Group-I received nebulization with 4 ml of 3% hypertonic saline and group-II received nebulization with 4 ml of 0.9% normal saline three times every day at intervals of 8 hours until they were improved enough for discharged²⁴. There was no detectable difference in color, smell, or other physical properties existed between 0.9% saline solution and 3% saline solution. Each of the two groups received the same supportive measures like propped up positioning, suction when needed, fluid, feeding, oxygen therapy (when oxygen saturation < 90%), paracetamol for fever, and counseling. All inhaled treatments were delivered to infants from standard air-compressed nebulizer. Following randomization and intervention, cases were monitored by respiratory distress assessment instrument (RDAI) score at 12 hourly intervals till the patient was ready for discharge. Oxygen saturation in room air and the time required from the initiation of the oxygen support to the withdrawal of oxygen therapy was recorded. Oxygen therapy was stopped when the patients breathed in the room air and maintaining $SP_{O_2} >95\%$ ²⁹. Length of hospital stay from admission to time taken to discharged was measured. The decision to discharge the patients was made in the morning rounds by the attending physician, based on clinical grounds alone. Prior permission was taken for this study from the Ethical Review Committee (ERC) of Dhaka Medical College & Hospital, Dhaka, Bangladesh. The outcome variables were (1) clinical severity score (2) length of hospital stay (3) oxygen saturation in room air (4) duration of oxygen supplementation (5) Side effects of drugs.

Collected data were processed and analyzed using computer software SPSS (Statistical Package for Social Sciences), version 19. The test statistics used to analyze the data presented on categorical scale were Chi-square or Fisher's Exact probability, while the data presented on continuous scale were analyzed using paired t-Test (for comparison data with group) and Unpaired t-Test (for comparison of data between groups). Level of significance was set 5% and p-value < 0.05 (at 95% CI) was considered significant.

Results

Ninety infant with bronchiolitis fulfill inclusion criteria included in the study between January 2013 and December 2013. About 29 (64.4%) of the children in Group-I(HS) were < 6 months old as opposed to 26 (57.7%) in Group-II(NS). Very few children were above the age 12 months. The mean age of the children were 5.2 ± 3.2 and 5.5 ± 3.0 months respectively with a male predominance in the both groups. There was no significant difference between the groups in term of age and sex ($p >0.05$) (Table – I).

Table I
Demographic characteristics between groups

Age in months	Group		p-value
	Group-I(HS) (n = 45)	Group-II(NS) (n = 45)	
< 6	29(64.4)	26(57.7)	
6-12	14(31.1)	15(33.3)	
>12	2(4.4)	4(8.8)	
Mean ± SD#	5.2 ± 3.2	5.5 ± 3.0	0.82
Sex *			
Male	25(55.5)	26(57.7)	0.50
Female	20(44.4)	19(42.2)	

All the cases in both the groups presented with runny nose, cough, breathing difficulty, chest in drawing and rhonchi but feeding difficulty was presenting feature in 25 (55.5%) cases in group- 1 and 26 (57.7%) cases in group –II. Wheezing was presenting feature in 42(93.33%) cases in group- 1 and 43(95.55%) cases in group-II. Only 6(6.66%) cases in group- I and 8(17.77%) cases in group -II presented with nasal flaring. In group-I 13(28.8%) cases and in group –II 12(26.66%) cases presented with fever. (Table-II).

Table-II*Clinical presentation of the cases on admission*

Clinical presentation	Group	
	Group -I(HS)	Group- II(NS)
Runny nose	45(100)	45(100)
Cough	45(100)	45(100)
Breathing difficulty	45(100)	45(100)
Feeding difficulty	25(55.5)	26(57.7)
Wheeze	42(93.33)	43(95.55)
Chest in-drawing	45(100)	45(100)
Nasal flaring	06(6.66)	08(17.77)
Tachypnoea	40(88.88)	39(86.66)
Tachycardia	41(91.11)	39(86.66)
Rhonchi	45(100)	45(100)
Fever	13(28.88)	94.9 ±1.7
Oxygen saturation	12(26.66)	94.6 ±2.6

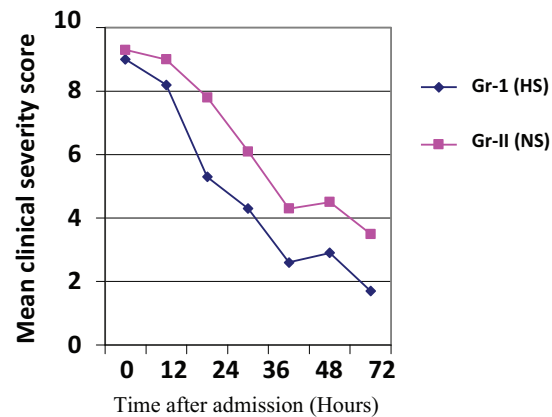
(mean± SD)

Baseline (on admission) clinical characteristics of the two study groups like respiratory rate score, wheezing score, retraction score, general condition score, clinical severity score were almost similar in both the groups ($p > 0.05$ in each case)(Table-III).

Table III*Comparison of baseline respiratory distress assessment instrument (RDAI) score*

Baseline characteristics	Group		p-value
	Group-I (HS) (n = 45)	Group-II (NS) (n = 45)	
Respiratory rate score	2.4±0.5	2.6±0.4	0.142
Wheezing score	2.1±0.5	2.0±0.3	0.193
Retraction score	2.0±0.5	2.0±0.6	0.859
General condition score	2.3±1.3	2.7±0.9	0.083
Clinical severity score	9.0±1.0	9.3 ±1.8	0.943

Mean clinical severity score at base line, at 12 hours, at 24 hours, at 36 hours, at 48 hours, at 60 hours, and at 72 hours in Group-I(HS) were 9.0, 8.2, 5.3, 4.3, 2.6, 2.9, 1.7 while in Group-II(NS) score were 9.3, 9.0, 7.8, 6.1, 6.1, 4.3, 4.5, 3.5 respectively.. Clinical severity score of both the treatment groups were reduced by three days but reduction was more significant in children who received 3% nebulised hypertonic saline (Figure- 1)

**Fig.-1:** Comparison of mean clinical severity score of two groups at 12 hourly intervals.

In Group-I (HS) 4 and in Group-II(NS) 5 patients required oxygen supplementation. The patients of Group-I on an average required 15 hours of oxygen therapy, while the patients of Group-II required 26.4 hours of oxygen therapy. Duration of oxygen therapy significantly reduced in Group- I compared to Group-II. (Table- IV)

Table IV*Comparison of duration of oxygen therapy between groups*

Duration of oxygen therapy	Group		p-value
	Group- I (HS) (n = 4)	Group -II (NS) (n = 5)	
Mean ± SD	15.0±6.0	26.4±5.4	0.02

Forty two (93.3%) of the children in Group-I were recovered by 72 hours and discharged from the hospital whereas 26(57.8%) of the children in Group-II were recovered and discharged during the same period ($p < 0.05$) (Table- V).

Table- V
Comparison of recovery and discharge from hospital between groups

Recovery and discharge	Group		p-value
	Group-I (n=45)	GroupII (n=45)	
Rapid (within 72 hours)	42(93.3)	26(57.8)	< 0.001
Gradual (after 72 hours)	3(6.7)	19(42.2)	

Length of hospital stay was significantly less in Group-I in comparison to group –II (p<0.05). (Table VI). 3% hypertonic saline nebulisation significantly reduced clinical severity, length of hospital stay and duration of oxygen therapy in case of acute bronchiolitis in comparison to 0.9% normal saline. Both the modalities of treatment were found to have no adverse effect.

Table VI
Comparison of Length of hospital stays between groups

Length of hospital stay(hrs)	Group		p-value
	Group- I (n = 45)	Group- II (n = 45)	
Mean clinical severity score			
Mean ± SD	58.1 ± 22.0	74.7 ± 27.2	0.002

Discussion

Bronchiolitis is a common problem in children less than two years of age and is the most common cause of hospitalization for respiratory infection in early childhood³⁻⁵. The present study was carried out to see whether 3% nebulised hypertonic saline reduce clinical severity and length of hospital stay in children with bronchiolitis than does 0.9% nebulised normal saline. The two study groups in the present study were almost similar with respect to their demographic characteristics like age and sex, baseline clinical characteristics, respiratory distress score like respiratory rate score, wheezing score, retraction score, general condition score, clinical severity score, and oxygen saturation in room air.

The study demonstrated that respiratory rate score, wheezing score, retraction score, general condition score and clinical severity score of both the treatment

groups were reduced and oxygen saturation in room air improved within three days but the reduction was much earlier in children who received 3% nebulised hypertonic saline than those who received 0.9% nebulised normal saline. The mean duration of oxygen supplementation was 9 hours shorter in the former group than that in the latter group. Majority (93.3%) of the 3% hypertonic saline group children recovered within 72 hours, where as 57.8% of the children of 0.9% saline group recovered from the disease during the same period. None of the patients in the present study encountered any side-effects. As all the pertinent baseline clinical characteristics of the two groups of children were similar, the differences in outcome between the groups (better outcome in 3% nebulised hypertonic saline) can be attributed to intervention.

In the present study 3% hypertonic saline significantly reduced length of hospital stay. Most patients in hypertonic saline group discharged within 3 days of treatment. Similar observation was seen in another study, mean length of hospital stay was shorter in hypertonic saline group³⁰. Supplementation of oxygen should be based on haemoglobin saturation. If haemoglobin saturation falls persistently below 90% in bronchiolitis patients, oxygen should be supplemented and may be discontinued if haemoglobin saturation is at or above 95% and the infant is feeding well and has minimal respiratory distress²⁹. In the present study the mean duration of oxygen supplementation was significantly shorter in the former group than that in the latter group. Almost similar observation was seen by Martin et al³¹.

Consistent with the findings of the present study several investigators have reported the use of hypertonic saline solution for infants in bronchiolitis with substantial benefits of therapy reported by many of them²¹⁻²². The investigators showed that nebulized hypertonic saline (HS) decreases the length of stay in the hospital (LOS) as compared with normal saline (NS) among infants hospitalized with the disease. Many of them used bronchiolitis severity score to evaluate patients over time and they found that inhaled 3% hypertonic saline with epinephrine administered by nebulization every 6-8 hours improved the bronchiolitis severity score and reduced the length of hospital stay in hospitalized patients when compared with 0.9% saline with epinephrine

20, 22-24. None of the studies reported any side-effects. These findings go in favour the findings of the present study as in the present study the mean length of hospital stay was much shorter (on an average 17 hours shorter) in the hypertonic saline group than that in the isotonic saline group.

A systematic review of four RCTs involving 254 infants with acute viral bronchiolitis (189 inpatients and 65 outpatients) concluded that nebulised 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score²⁴. However, an orthodox finding was reported by another small RCT which investigated the use of hypertonic saline in the emergency department setting, and the authors suggested that immediate clinical benefits may not be seen with nebulised hypertonic saline³².

Airway oedema and mucus plugging are the predominant pathological features in acute viral bronchiolitis. Hypertonic saline decreases airway oedema, improves mucus rheologic properties and mucociliary clearance, and thus decreases airway obstruction³³. It is thought that hypertonic saline facilitates removal of inspissated mucus through osmotic hydration, disruption of mucus strand cross-linking and reduction of mucosal oedema^{34, 35}.

In summary in this study both treatment groups demonstrated clear evidence of clinical improvement and oxygen saturation but 3% hypertonic saline group in comparison with 0.9% normal saline group showed more efficacy in relieving symptom, improving oxygenation and reducing length of hospital stay in infant with acute bronchiolitis. It seems that the use of nebulized

3% hypertonic saline in children admitted with moderate to severe viral bronchiolitis is a safe and effective therapy. This modality being cheap intervention has enormous potential for cost saving both in developing and developed countries, more so, for it reduces the length of hospital stay as evidenced by the findings of the present study and as suggested by a recent Cochrane review²⁴. Early, prehospital intervention for bronchiolitis with this safe, effective, and inexpensive agent might save lives, reduce complications and hospitalizations, and can be use where hospital care is not available.

Finally, it can be stated that in 1963, Reynolds and Cook stated that "oxygen is vitally important in bronchiolitis and there is little convincing evidence

that any other therapy is consistently or even occasionally useful"³⁶. Now, fifty years later, supportive care including administration of oxygen and fluids still is the cornerstone of treatment of acute viral bronchiolitis. To this supportive care,

Conclusion

The study concluded that 3% hypertonic saline nebulisation significantly reduced clinical severity, length of hospital stay and duration of oxygen therapy in case of acute bronchiolitis in comparison to 0.9% normal saline. Both the modalities of treatment were found to have no adverse effect.

Recommendation

A multicentre study with large sample size should be carried out to validate the use of 3% hypertonic saline nebulisation in reducing clinical severity and length of hospital stay in bronchiolitis.

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