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A Comparative Study of Nebulized 3% Hypertonic Saline Versus Nebulized Adrenaline in The Treatment of Acute Bronchiolitis

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Abstract

Background: Acute bronchiolitis is the most common lower respiratory tract infection in young infants and young children. The respiratory syncytial virus is the commonest cause of bronchiolitis. Recently the role of nebulized 3% saline has come into focus. Nebulized adrenaline has also been suggested as another treatment option, its primary role being the reduction of mucosal edema, which is an important part of the disease pathology in bronchiolitis. Objective: To see the effects of nebulized adrenaline in comparison to nebulized 3% hypertonic saline in the treatment of acute bronchiolitis. **Material & Methods:** This was a randomized controlled trial, carried out in the Department of Pediatrics, Bangladesh Shishu Hospital and Institute from October 2017 to March 2020. A total of 90 children from 1 month to 2 years of age of either sex who were diagnosed and admitted with acute bronchiolitis were enrolled. After enrollment, they were randomly assigned to either 3% nebulized hypertonic saline (group A=45) or to the nebulized adrenaline-1:1000 group (group B=45). Monitoring was done by respiratory distress assessment instrument (RDAI) score at 12 hours interval for 1st 24 hours and then 24 hourly till the patient was ready for discharge. The efficacy was determined by assessing clinical severity score/RDAI score and length of hospital stay. Data were analyzed using SPSS version-23. **Results:** The mean age was found 6.34±3.89 months in group A and 6.06±3.55 months in group B. The majority of patients were males in both groups. All patients had a cough, breathing difficulty, Ronchi, and chest indrawing in both groups. Changes in heart rate were 5.68±6.61/min in group A and 2.86±5.87/min in group B, which was significantly decreasing in group A than in group B. Mean clinical severity scores at 12 hours and at 24 hours were statistically significant ($p<0.05$). However, mean clinical severity scores at baseline, at 48 hours, at 72 hours, and at 96 hours were not statistically significant. The mean duration of oxygen therapy was found 15.00±5.36 hours in group A and 24.63±11.64 hours in group B. Which indicates that the duration of oxygen therapy was significantly higher in group B than in group A. Majority of the patients of group A and group B were discharged within 72 hours 39(86.7%) and 28(62.2%) respectively, which was statistically significant. **Conclusions:** Nebulization with 3% hypertonic saline significantly reduced clinical severity score and length of hospital stay in case of acute bronchiolitis in comparison to nebulized adrenaline.

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Keywords:- Acute bronchitis, 3% hypertonic saline, Nebulized adrenaline.

INTRODUCTION

Bronchiolitis is an acute inflammation of the bronchioles that leads to small airway edema, necrosis, and increased mucus production. The American Academy of Pediatrics (APP) guidelines define bronchiolitis as a viral upper respiratory infection prodrome followed by respiratory effort and wheezing in children younger than 2 years of age.[1] According to the national guideline of Bangladesh, bronchiolitis is a clinical diagnosis characterized by cough and respiratory distress associated with wheeze, preceded by a runny nose with or without fever in young children below 2 years of age, particularly between 2-6 months of age.[2] It is a viral disease caused by Respiratory Syncytial Virus (RSV), Human Parainfluenza virus, Rhinovirus, Human metapneumovirus, Influenza virus, Coronavirus, Human bocavirus, Adenovirus, and Mycoplasma pneumonia.[3] In a nationwide hospital prevalence study, conducted over 43 hospitals in Bangladesh on 5157 children, it was found that 21% of under-five children suffer from bronchiolitis and 11.5% from pneumonia (Kabir 2009). Bronchiolitis most commonly occurs in the younger infant and almost never beyond 2 years. Incidence is most common in the winter months, from December to March in northern India.[4] Ninety percent of children are infected with RSV in the first 2 years of life, and up to 40% of them will have a lower respiratory infection. Infection with RSV does not grant permanent or long-term immunity. Reinfections are common and may be experienced throughout life.[5] Acute bronchiolitis usually occurs following exposure to a patient with minor respiratory symptoms within the previous week. The infant first develops a mild upper respiratory tract infection with sneezing and rhinorrhea. This is followed by decreased appetite and moderate grade fever. After a few days' respiratory distress ensues. The infant is often tachypneic, which may interfere with feeding. The physical examination is characterized most prominently by wheezing, prolonged expiration, fine rales, and rhonchi. The work of breathing increases characterized by nasal flaring, intercostal and subcostal retractions, hyper expansion of the chest, restlessness, and peripheral cyanosis.[6] Most infants show improvement within 3-4 days after the onset of the disease but the cough may persist for the next few weeks.[7] The source of viral infection is usually a family member with a minor respiratory illness. Infants whose mothers smoke cigarettes are more likely to acquire bronchiolitis than infants with non-smoking mothers. The occurrence is more observed where a heavy smoker stays with children.[8] Approximately 100,000 bronchiolitis hospital admissions occur annually in the United States, leading to an estimated cost of $1.73 billion.[9] The mortality rate is 0.5-1.5% among hospitalized infants but increases to 3-4% for infants with potential pulmonary or cardiac diseases.[10] The diagnosis is usually a clinical one and investigations are not generally needed to confirm it. However, confirmation of RSV infection can be made by Enzyme-linked Immunofluorescence Assay (ELISA) and fluorescent antibody techniques for detection of the viral antigen, and amplification of the virus using the shell vial method, and amplification of viral genome by Polymerase Chain Reaction

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(PCR) or viral culture. A Rapid Test using monoclonal antibodies against RSV on nasopharyngeal aspirates can identify RSV at the bedside.[11] Management of bronchiolitis is often frustrating for physicians and caregivers because 'nothing seems to work' in most cases.[12] There is no effective and universally accepted treatment for bronchiolitis. Treatment of bronchiolitis is still mainly supportive. Pharmacologic options include oxygen (O2) therapy; beta$_2$-adrenergic agonists, albuterol and levalbuterol; racemic epinephrine; corticosteroids; antibiotics; and, recently, hypertonic saline. Oxygen therapy provides oxygen to the lungs and acts as a direct bronchodilator. Current AAP guidelines recommend the use of supplemental oxygen if oxygen saturations are less than 90% in order to avoid hypoxemia.[13] Hypertonic saline shifts the flow of water into the mucus layer by osmosis, reducing submucosal edema, reducing the viscosity of mucus, improving mucus clearance, and rehydrating the air surface liquid.[14,15,16] The updated AAP guidelines support the use of hypertonic saline nebulization for infants and children hospitalized for bronchiolitis. Racemic epinephrine should be a useful therapeutic option as a result of its agonistic effects on alpha and beta receptors, helping to reduce edema and mucus plugging. As a result of possible improvement in patients with severe bronchiolitis, the 2014 AAP guidelines provided some support for racemic epinephrine as a rescue agent in the hospital setting conducted a study where they commented that adrenaline nebulization in infants with moderate to severe bronchiolitis is superior to salbutamol nebulization.[17,18,19] In their study, the oxygen requirement and time at which the children were fit for discharge, was significantly shorter in the adrenaline group. When comparative efficacy was evaluated, it was observed that nebulized l-adrenaline was superior to nebulized salbutamol in bronchiolitis. They commented that nebulized adrenaline can be safely used in reliving of symptoms in bronchiolitis without any major side effects. In a prospective study on the efficacy of nebulized 3% hypertonic saline versus 0.9% normal saline in hospitalized infants with bronchiolitis.[20] They observed that nebulized 3% hypertonic saline decrease the baseline clinical severity score of bronchiolitis faster than 0.9% normal saline.

OBJECTIVES

General objective:

To see the effects of nebulized adrenaline in comparison to nebulized 3% hypertonic saline in the treatment of acute bronchiolitis.

Specific Objectives:

To find out the clinical recovery and length of hospital stay in the nebulized adrenaline group. To find out the clinical recovery and length of hospital stay in the nebulized 3% hypertonic saline group. To compare two groups.

MATERIAL AND METHODS

It was a randomized controlled study. Conducted at Bangladesh Shishu Hospital and Institute, Dhaka. Bangladesh, from October 2017 to March 2020. All children having acute bronchiolitis were admitted to Bangladesh Shishu Hospital and Institute, Dhaka. Bangladesh at a defined period. A total of 90 patients with acute bronchiolitis were included

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in this study. The two groups were randomly assigned to nebulized 3% hypertonic saline (n=45) and nebulized 1:1000 adrenaline (n=45).

Inclusion criteria:

- Age group 1 month to 2 years.
- First episode of wheezing.
- History of viral prodrome present.
- No history of treatment with either nebulized 3% hypertonic saline or nebulized adrenaline during the disease course.

Exclusion criteria:

- Age group <1 month or >2 years.
- History of two or more episodes of respiratory distress in the past.
- Family history of Asthma.
- Congenital heart disease or chronic lung disease.

After admission to the hospital, a details history was taken from the patient/attendant and a thorough physical examination was done. Oxygen saturation in room air and RDAI score were measured and recorded on admission as baseline characteristics. Oxygen saturation was measured by using a noninvasive pulse oximeter. The following investigations were performed on all patients:

- Hb %, total leucocyte count, differential leukocyte count
- X-ray chest PA view at the time of admission.

History of cough, breathing difficulty, chest in drawing, fever, and wheezing following a viral upper respiratory tract infection were taken. Respiratory rate, auscultator findings (Ronchi), retraction, and general condition were assessed by using Respiratory Distress Assessment Instrument (RDAI) described by.10 After taking written informed consent drug was given according to the dosing schedule. Group-A received nebulization with 4 ml of 3% hypertonic saline and Group B received nebulization with 1 ml of adrenaline (1:1000) mixed with 3 ml normal saline four times every day at intervals of 6 hours until they were improved enough for discharge. Each of the two groups received the same supportive measures like propped-up positioning, suction when needed, fluid, feeding, and oxygen therapy score at 12 hours interval for 1st 24 hours and then 24 hours 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 were recorded. Oxygen therapy was stopped when the patients breathed in the room air and maintained SP02 >95%. Length of hospital stay from admission to the time taken to discharge was measured. Statistical analysis was carried out using the SPSS version 23.0. The Chi-square test was used for categorical variables. Unpaired t-test and paired t-test were used for continuous variables. P values <0.05 were considered statistically significant. Ethical clearance was taken from the ethical review committee of Bangladesh Shishu Hospital and Institute. Informed written consent was taken from parents or legal guardians.

RESULTS

[Table 1] showed the majority of patients belonged to age 1-6 months in both groups, which was 28(62.2%) in group A and 26(57.8%) in group B. The mean age was found 6.34±3.89 months in group A and 6.06±3.55 months in group B. The mean difference was not

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statistically significant (p>0.05) between groups. Males were predominant in both groups, which were 35(77.8%) in group A and 32(71.1%) in group B. Whereas females were 10(22.2%) and 13(28.9%) in group A and group B respectively. The differences were not statistically significant (p>0.05) between the groups.

[Table 2] showed all patients had a cough, breathing difficulty, Ronchi, and chest in drawing in both groups. Fever was found at 40(88.9%) in group A and 36(80.0%) in group B. Runny nose was 42(93.3%) in group A and 43(95.6%) in group B. Feeding difficulty was found at 35(77.8%) and 30(66.7%) in group A and group B respectively. Wheeze was found in 38(84.4%) in group A and 36(80.0%) in group B. The difference was not statistically significant (p>0.05) between the groups.

[Table 3] showed the initial and 24 hours after nebulization means heart rate, which was not statistically significant when compared between the two groups. Changes in heart rate were 5.68±6.61/min in group A and 2.86±5.87/min in group B, which was significantly decreasing in group A than in group B. Initial and 24 hours after nebulization mean SPO2 was not statistically significant when compared between the two groups. Changes in SPO2 were slightly more in group A than in group B but were not statistically significant (p>0.05) between groups.

[Table 4] showed mean clinical severity score/RDAI score at 12 hours and at 24 hours were statistically significant (p<0.05) when compared between group A vs group B. However, mean clinical severity scores at baseline, at 48 hours, at 72 hours, and at 96 hours were not statistically significant between groups.

[Table 5] showed that the mean duration of oxygen therapy was found 15.00±5.36 hours in group A and 24.63±11.64 hours in group B. This indicates that the duration of oxygen therapy was significantly higher in group B than in group A.

[Table 6] showed that majority of the patients of group A and group B were discharged within 72 hours. That was 39(86.7%) and 28(62.2%) from group A and group B respectively which was statistically significant when compared between groups.

[Table 7] showed that the mean length of hospital stay was 42.77±29.02 hours in group A and 59.26±32.64 hours in group B which indicate that the length of hospital stay was significantly higher in group B than in group A.

Table 1: Distribution of the study patients by demographic variables (N=90)

Demographic variables	**Group A (n=45)**		**Group B (n=45)**		**P-value**
	n	**%**	**n**	**%**	
Age group (months)					
1-6 months	28	62.2	26	57.8	0.724ns
6-12 months	10	22.2	14	31.1	
12-24 months	7	15.6	5	11.1	
Mean ±SD	6.34±3.89		6.06±3.55		
Gender					

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Male Child	35	77.8	32	71.1	0.468
Female Child	10	22.2	13	28.9	

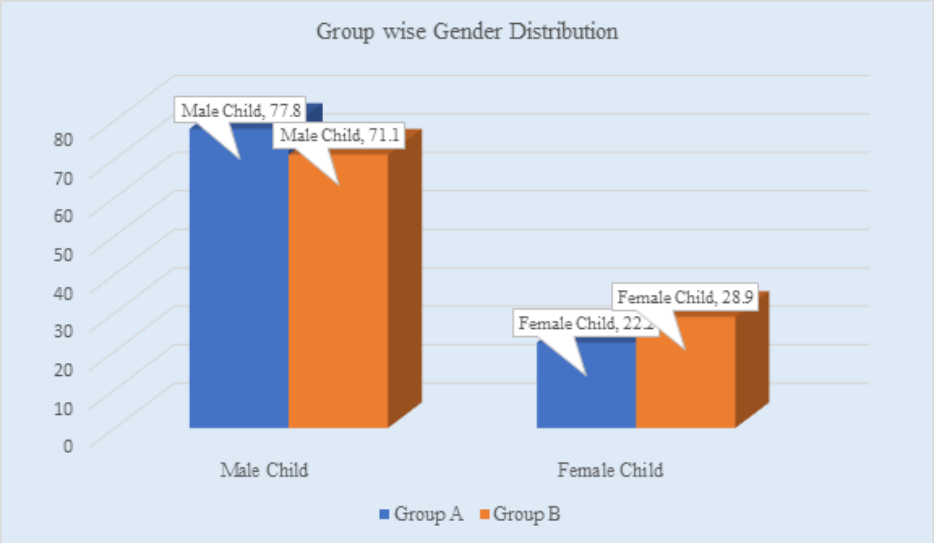

Figure 1: Group-wise Gender Distribution (N=90)

Table 2: Distribution of the study patients by clinical features (N=90)

Clinical features	**Group A (n=45)**		**Group B (n=45)**		**P-value**
	n	**%**	**n**	**%**	
Cough	45	100.0	45	100.0	-
Fever	40	88.9	36	80.0	0.245^{ns}
Runny nose	42	93.3	43	95.6	0.500^{ns}
Difficulty in breathing	45	100.0	45	100.0	-
Feeding difficulty	35	77.8	30	66.7	0.229^{ns}
Irritability	10	22.2	13	28.9	0.468^{ns}
Lethargic	12	26.7	14	31.1	0.641^{ns}
Wheeze	38	84.4	36	80.0	0.581^{ns}
Ronchi	45	100.0	45	100.0	-
Chest in drawing	45	100.0	45	100.0	-
Nasal flaring	20	44.4	15	33.3	0.279^{ns}
Tachypnea	4	8.9	6	13.3	0.502^{ns}
Tachycardia	16	35.6	11	24.4	0.250^{ns}

Table 3: Improvement of HR and SPO2 after 24 hours of nebulization (N=90)

Physical examination	**Group A (n=45)**	**Group B (n=45)**	**P-value**
	Mean ±SD	**Mean ±SD**	
Heart rate (/min)			
Initial	132.06±8.68	129.86±9.18	0.246ns

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24 hours after nebulization	126.37±6.98	127.00±6.02	0.652ns
Changes HR	5.68±6.61	2.86±5.87	0.035s
SPO2 (%)			
Initial	90.22±5.40	91.33±5.83	0.351ns
24 hours after nebulization	95.68±2.92	96.62±2.89	0.132ns
Changes SPO2	5.46±3.62	5.28±3.83	0.822ns

Table 4: Mean respiratory distress assessment instrument (RDAI) score Among Two Group (N=90)

Mean RDAI score	**Group A (n=45)**	**Group B (n=45)**	**P-value**
	Mean ±SD	**Mean ±SD**	
At baseline	7.88±1.58	7.66±1.41	0.485ns
At 12 hours	4.64±1.36	5.26±1.33	0.032s
At 24 hours	3.23±1.51	4.24±1.28	0.001s
At 48 hours	3.02±1.11	3.43±1.30	0.625ns
At 72 hours	2.69±1.54	3.20±1.20	0.339ns
At 96 hours	1.66±0.51	2.00±0.75	0.373ns

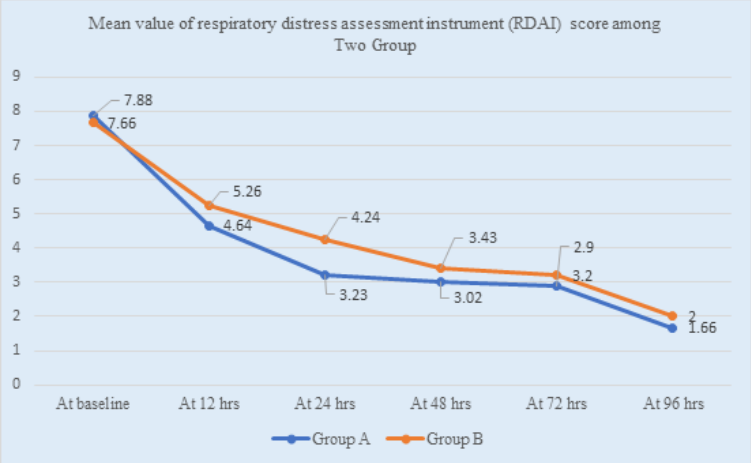

Figure 2: Mean value of respiratory distress assessment instrument (RDAI) score Among Two Group (N=90)

Table 5: Comparison of duration of oxygen therapy between groups (n=35)

	Group A (n=16)	**Group B (n=19)**	**P-value**
	Mean ±SD	**Mean ±SD**	
Duration of oxygen therapy (hours)	15.00±5.36	24.63±11.64	0.005s

Table 6: Comparison of recovery and discharge from hospital between two groups (N=90)

Recovery and discharge	**Group A (n=45)**		**Group B (n=45)**		**P-value**
	n	**%**	**n**	**%**	
Rapid (within 72 hours)	39	86.7	28	62.2	0.007s
Gradual (after 72 hours)	6	13.3	17	37.8	

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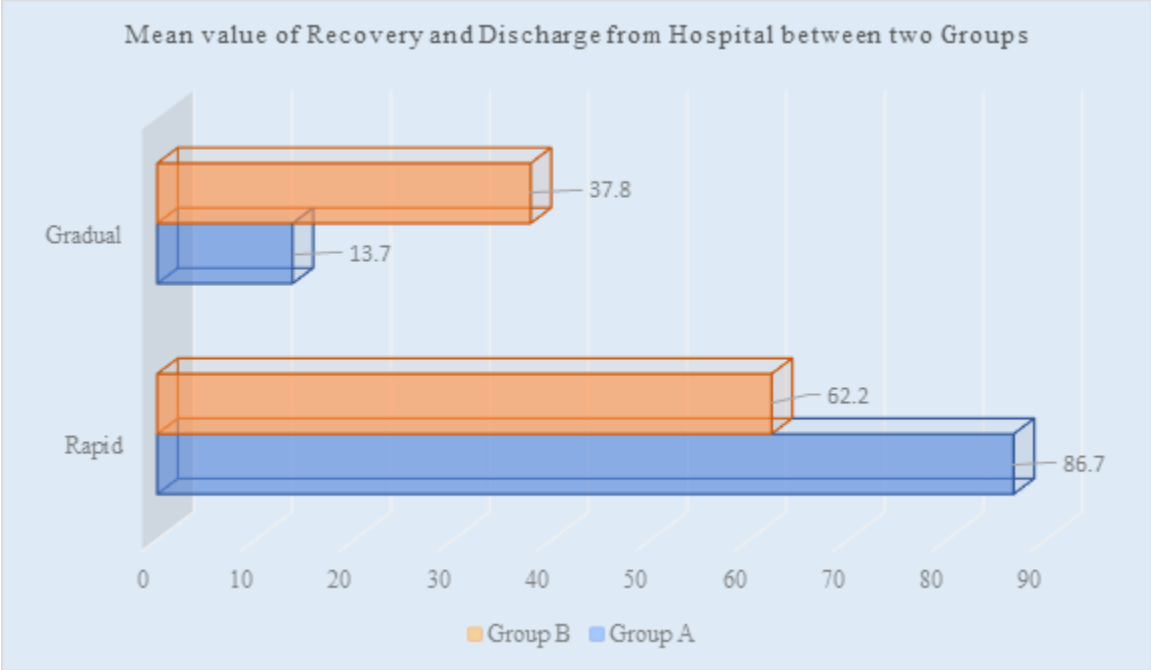

Figure 3: Mean value of Recovery and Discharge from Hospital between two Groups (N=90)

Table 7: Comparison of length of hospital stays between groups (N=90)

	Group A (n=45)	**Group B (n=45)**	**P-value**
	Mean ±SD	**Mean ±SD**	
Length of hospital stay (hours)	42.77±29.02	59.26±32.64	0.013s

DISCUSSION

This study was carried out in the Department of Pediatrics of Dhaka Shishu (Children) Hospital, Dhaka. 90 patients of 1-24 months of age with acute bronchiolitis were included in this study. In this study, the majority of patients belonged to age 1-6 months in both groups, which were 28(62.2%) in group A and 26(57.8%) in group B. The mean age was found 6.34±3.89 months in group A and 6.06±3.55 months in group B. The mean difference was not statistically significant (p>0.05) between the two groups. In a study, the mean age was 6.03±3.71 months in the hypertonic saline group and 5.69±3.34 months in the normal saline group.[11] It had been reported in a study that the mean age was 4.4±3.4 months in the hypertonic saline group and 5.5±3.9 months in the normal saline group.[21] The difference was not statistically significant (p>0.05) between the groups. In a study, it had been found that out of 50 patients included in either treatment group, the majority were of age group 1-6 months.[22] This number was 68% and 80% in hypertonic saline and adrenaline groups respectively. This was consistent with other studies in which the majority of infants were also from the same age group.[23,24,25] Other studies like found the mean age between 6-12 months.[26,27] The infants with

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RSV infection in this age group have a greater propensity to wheeze because of the small caliber of airways. The resistance to airflow is more as it varies as the 4th power of the radius of the airway. Since our diagnosis in this study was based on the auscultator finding of wheezing, this was consistent with the majority of infants being included in the age group 1-6 months. The number decreased progressively in the age group 6-12 months and 1-2 years as airways grow in size and the propensity to wheeze decreased. In this study, we observed that the males were predominant in both groups, which were 35(77.8%) in group A and 32(71.1%) in group B, whereas females were 10(22.2%) and 13(28.9%) in group A and group B respectively. The difference was not statistically significant ($p>0.05$) between the two groups. This is in accordance with the known fact that bronchiolitis affects more males as compared to females. The high incidence of acute bronchiolitis in males as compared to females may be attributed to the presence of two X chromosomes which provide greater genetic diversity to the female immunologic defenses.[28] It could also be due to the greater healthcare-seeking attitude of parents towards the male child in the Indian Subcontinent. In this study all patients had a cough, breathing difficulty, Ronchi, and chest indrawing in both groups. Fever was found at 40(88.9%) in group A and 36(80.0%) in group B. Runny nose was 42(93.3%) in group A and 43(95.6%) in group B. Feeding difficulty was 35(77.8%) and 30(66.7%) in group A and group B respectively. Wheezing was found in 38(84.4%) in group A and 36(80.0%) in group B. The difference was not statistically significant ($p>0.05$) between the two groups. In the comparison of the clinical presentation of two previous studies, it has been found that cough (98% and 100%), fever (75% and 67.7%), and fast breathing (90% and 100%) were the predominant symptoms.[29,30] Tachypnea signs of viral illness like nasal catarrh and on auscultation rhonchi and scattered rales are the predominant findings. In this present study, we found that the mean disease duration before admission was 3.28±1.23 days in group A and 3.33±1.18 days in group B. In the present study initial and 24 hours after nebulization mean heart rate, which was not statistically significant when compared between the two groups. Changes in heart rate were 5.68±6.61/min in group A and 2.86±5.87/min in group B, which was significantly decreasing in group A than in group B. Initial and 24 hours after nebulization mean SPO_2 was not statistically significant when compared between the two groups. Changes in SPO_2 were slightly more in group A than in group B, but not statistically significant ($p>0.05$). According to a previous study, there was no significant difference between a change in heart rate before and after treatment with 3% hypertonic saline alone or 3% hypertonic saline plus 1:1000 adrenaline.[31] The change in heart rate was 18.87 and 20.53 in the first and second groups respectively with a p-value of 0.898. Similar to our results, it had been found in some previous study, no significant increase in heart rate in patients treated with nebulized epinephrine compared to placebo or another bronchodilator.[32,33,34] Unlike our results, it had been found a significant increase in heart rate after treatment with nebulized epinephrine, an increase of 7-21 beats per minute with a significant level of ≤ 0.05.[35,36] On the other hand, in a study it had been found a decrease in heart rate after treatment with nebulized racemic epinephrine compared to placebo.[37] As

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respiratory distress decreased after nebulization and the patient became quiet so heart rate decreased. Due to the adrenergic effect of adrenaline heart rate decreased less in the adrenaline group. In this study, we observed that mean clinical severity scores at 12 hours and at 24 hours were statistically significant ($p<0.05$) when compared between the two groups. However, mean clinical severity scores at baseline, at 48 hours, at 72 hours, and at 96 hours were not statistically significant between the two groups. It had been observed that maximum recovery occurred in the adrenaline group (48%) in the second week while in the hypertonic saline group, maximum recovery occurred in the first week.[38] On statistical analysis, the p-value was (<0.001) which was statistically significant. Besides having a common mechanism of action for decreasing airway edema, hypertonic saline and adrenaline differ in other functions. 3% hypertonic saline is known to improve mucus clearance, increase coughing action, make the mucus less viscous, increase ciliary action as well as decrease bacterial colonization. Adrenaline on the other hand acts by vasoconstriction and decreases airway edema and inflammation. It is perhaps due to these additional mechanisms of action that hypertonic saline showed more efficacy in our study during treatment. In this study, it was observed that the mean duration of oxygen therapy was 15.00±5.36 hours in group A and 24.63±11.64 hours in group B. Which indicate that the duration of oxygen therapy was significantly higher in group B than in group A. In this current study, it was observed that the majority of the patients of group A and group B were discharged within 72 hours. That is 39(86.7%) and 28(62.2%) from group A and group B respectively. Which was statistically significant. It had been observed in a previous study the mean duration of hospital stay was 6±1.2 and 7.4±1.5 days in 3% hypertonic saline and 0.9% normal saline groups respectively which was also statistically significant ($p<0.05$).[39] However, the difference was not statistically significant. Perhaps hospital stay was influenced by other factors like the transition to oral feeding, gaining proper appetites, and ensuring weight gain before discharge. Associated factors like feeding habits, use of top feeds, anemia, etc. also played a role in these infants' prolonged hospital stay.

Limitations of The Study

Though the sample size was small therefore, in the future, further studies may be undertaken with a large sample size most cases there was an overlapping of many predictors. So, the exact predictor could not be evaluated. The study population was selected from one selected hospital in Dhaka city, so the results of the study may not reflect the exact picture of the entire country. Bronchilitis was diagnosed clinically. No confirmatory investigation was done.

CONCLUSIONS

The study concluded that both nebulized 3% hypertonic saline and nebulized adrenaline are useful in relieving symptoms and improving oxygenation in acute bronchiolitis. When comparative efficacy was evaluated, it was observed that nebulized 3% hypertonic saline is a better treatment modality in comparison to nebulized adrenaline in acute bronchiolitis. Infants treated with 3% hypertonic saline showed greater improvement and early hospital discharge.

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Recommendations

Nebulized 3% hypertonic saline can be safely used in reliving of symptoms in bronchiolitis without any side effects. Larger, multicenter, double-blind, randomized controlled trials are required to validate this study's results.

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