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Comparing Treatment with Nebulized 3% Hypertonic Saline Versus Nebulized 0.9% Saline In Patients With Acute Bronchiolitis: A Double-Blind Randomized Controlled Trial

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Abstract

Objective: To establish the therapeutic role of nebulized hypertonic saline solution in the management of acute bronchiolitis in terms of primary and secondary outcomes.

Methods: This randomized control trial was conducted in the Pediatric department of Holy Family Hospital, Rawalpindi for 8 months from September 2021 to April 2022 after ethical approval. A total of 65 cases of acute bronchiolitis were enrolled who were divided into two groups. The intervention group was nebulized with 3 ml of 3% hypertonic saline 6 hourly while the control group was nebulized with 0.9% saline 6 hourly during hospital stay in addition to the standard treatment. Children in both groups were monitored in terms of clinical severity score, feeding, hydration status, length of hospital stay, duration of oxygen supplementation, development of any adverse effect, and outcome (length of hospital stay and clinical severity score) was observed. Data was collected on a predesigned proforma, and SPSS version 21 was used to analyze the data.

Results: Two groups were comparable for age, gender, and baseline characteristics including clinical severity score. Length of hospital stay was significantly less in the hypertonic saline group 75.53 ±43 .87 versus 45.92 ± 12.19 (p-value 0.000). Similarly, in patients requiring oxygen, treatment with hypertonic saline significantly reduced the duration of nebulization, 27.21 ±26.20 versus 10.67± 7.91 (p-value 0.03). However clinical severity score between the two groups was not different, 5.42 ± 2.88 in the saline group and 4.50 ± 2.88 p value 0.921.

Conclusion: Nebulization with hypertonic saline reduces oxygen requirement and benefits in reducing the length of hospital stay.

Keywords: Bronchiolitis, Hypertonic saline (HS), Normal saline (NS).

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1. Introduction

Acute bronchiolitis is a viral infection of the lower respiratory tract and one of the most substantial health burdens for infants and young children worldwide.[1] The most prevalent cause of bronchiolitis in infants is Respiratory syncytial virus(RSV).[2] Global burden of disease in 2019 is estimated 50 million cases of lower respiratory tract infection under 5 years of age accounting bronchiolitis as an important cause after pneumonia.[1] Many children of bronchiolitis do not require hospital admission, only 3% of them are hospitalized out of 18% of total hospital admissions in infants.[3] Pathophysiology of bronchiolitis is characterized by extensive inflammation and oedema of the small airways, increased mucus production, necrosis, and destruction of airway epithelial cells. The destruction of cells starts an inflammatory response causing polymorphonuclear cells and lymphocyte proliferation. The submucosa and adventitial tissues become edematous with increased mucus secretion. Mucus plugs lead to bronchiolar obstruction, air trapping, and different degrees of lobar collapse.[4,5]

The standard treatment for acute bronchiolitis remains supportive care including adequate oxygen exchange, hydration, and feeding of the infant. The use of hypertonic saline in bronchiolitis was recommended by the American Academy of Pediatrics guidelines in 2014. Hypertonic saline is hyperosmolar and when it is nebulized, it absorbs water from the mucosal and submucosal space and increases mucociliary function by clearing both fluid and mucus plugs accumulated in the lung airways of infants with bronchiolitis.[6]

One randomized trial demonstrated a significant reduction in the length of hospital stay and improved clinical severity score in infants with the use of nebulized 3% saline in acutebronchiolitis.[7] A large meta-analysis was conducted on 24 trials in 2017 showed hypertonic saline modestly reduced length of

hospital stay and improved clinical severity score in patients admitted with acute bronchiolitis.[8]

A multicentre RCT revealed hypertonic saline had no clinical benefit in reducing the length of hospital stay in patients admitted with bronchiolitis and is not a cost-effective therapy.[9]

Most local clinical trial results reveal hypertonic saline is an effective modality in the treatment of children with acute bronchiolitis, a clinical trial conducted in the pediatric department of Nishtar Hospital, Multan in 2017 concluded that hypertonic saline resulted in significant reductions in modified respiratory assessment score (MRAS) and hospital stay as compared to normal saline in children with acute bronchiolitis.[10] Another trial in Children's Hospital and Institute of Child Health, Lahore, Pakistan, showed a mean reduction in respiratory score was significantly higher in patients of acute bronchiolitis treated with hypertonic saline(3%) as compared to normal saline (0.9%).[11]

There is heterogenicity in the results of different clinical trials as well as in guidelines. The theoretical benefits provide the rationale for the treatment of acute bronchiolitis with nebulized hypertonic saline solution. This study aims to establish the therapeutic role of nebulized hypertonic saline solution in the management of acute bronchiolitis as assessed by clinically relevant outcomes. This modality can provide a cheap and effective therapy for children with acute bronchiolitis.

2. Materials & Methods

This clinical control trial was done in the Pediatric department of Holy Family Hospital, Rawalpindi for a period of 8 months from September 2021 to April 2022 after ethical approval.

The sample size was estimated from the previous study [10]. According to this study mean length of hospital stay was 4.47 ± 1.3 days in the saline group and 3.47 ±0.89 days in the hypertonic group which corresponds to a large Cohen d effect size of 1.03 while detecting this effect size with a 95% confidence interval and 80 % power of study required 30 patients. However, we took 64 patients, of which 38 patients received nebulization with saline and 26 patients were nebulized with the hypertonic saline group. Inclusion & Exclusion criteria: Children between 3 to 24 months diagnosed with acute bronchiolitis of both genders who were admitted due to mild to moderate respiratory distress based on clinical severity score, hypoxia (oxygen saturation ≤ 92%), decreased feeding and/or dehydration and unreliable caregiver to ensure patient care and appropriate follow-up were included. Children with severe bronchiolitis requiring respiratory support with invasive or non-invasive modalities i.e., ventilator and CPAP with a history of recurrent wheezing, family and/or personal history of atopy, with other comorbidities such as congenital respiratory tract disease, congenital heart disease and any known immunodeficiency, children born preterm (<32 weeks) and with history of apnea were excluded.

Children in group 1 were nebulized with 3 ml of 3% hypertonic saline 6 hourly whereas children in group 2 were nebulized with 0.9% saline 6 hourly during hospital stay in addition to the standard treatment provided according to hospital protocols for children admitted with bronchiolitis.

Data was collected after ethical approval from the ethical committee and informed consent from parents. Children in both groups were monitored in terms of clinical severity score, feeding, hydration status, length of hospital stay, duration of oxygen supplementation, and development of any adverse effect.

Data was collected on a predesigned proforma and then entered manually in SPSS 21 for statistical analysis. Qualitative variables such as gender, feeding, dehydration, adverse events, and outcome were measured as frequency and percentages. Quantitative variables such as age, length of hospital stay, clinical severity score, and duration of oxygen supplementation were measured as Mean and standard deviation. An Independent t-test was used to compare quantitative variables between the two groups while chi-square was used for nominal data. A two-sided hypothesis with a 95% confidence level p-value ≤ 0.05 was taken as significant.

3. Results

During this study period, 65 patients were admitted for acute bronchiolitis. 26 patients received hypertonic saline for nebulization while 38 patients received normal saline for nebulization. There were no significant differences in age or gender between the two groups.

Table 2 shows baseline characteristics between the two groups which include clinical severity score, dehydration and feeding status, and whether oxygen was

needed between two groups. Most of the patients 52 (82.8%) had CSS scores 6 and above at baseline.

Table 1: Demographic and Baseline characteristics of the study subjects

Groups		1 (Saline)	2 (Hypertonic saline)	P value
Counts		N =38	N =26	
Gender				0.362
Male	35 54.70%	19 50.0%	16 61.5%	
Female	29 45.30%	19 50.0%	10 38.5%	
Age in months mean (SD)		7.26 ± 7.37	8.46±6.31	0.502

There was no significant difference in mean CSS score at baseline p value 0.663 or CSS category score 6 and above between the two groups, p-value 0.88. A total of 43 (67.2%) patients needed oxygen for the presentation. Feeding status was not well in most of the patients 45 (70.3%) while 32 (50%) patients were dehydrated. None of the clinical characteristics showed significant differences between the two groups. (Table 2)

Table 2: Baseline clinical characteristics of two study groups

	Count	Saline	Hypertonic	P value
CSS baseline Mean (SD)		8.92 ± 2.97	8.58±3.52	.663(a)
CSS baseline (categorical)				0.88 (b)
mild	11 17.2%	4 10.5%	7 26.9%	
6 and above	52 82.8%	34 89.5%	18 73.1.%	
Oxygen needed				0.799(b)
no	21 32.8%	12 31.6%	9 34.6%	
yes	43 67.2%	26 68.4%	17 65.4%	
Feeding status				0.168(b)
Average	13 20.3%	5 13.2%	8 30.8%	
Not well	45 70.3%	30 78.9%	15 57.7%	
well	6 9.37%	3 7.9%	3 26.6%	
Dehydration				0.611(b)
Present	32 50%	20 52.6%	12 46.2%	
Absent	32 50%	18 47.4%	14 53.8%	

CSS clinical severity score
An independent t-test, chi-square test

The study findings showed length (hours) was 75.53 ±43.87 in the saline group which reduced significantly in the hypertonic saline group 45 .92± 12.19 p-value 0.000. This corresponds to Cohen d effect size of 0.92. Of the 43 patients who needed oxygen, 26 were in the saline group and 17 were in the hypertonic saline group. The study finding showed that the mean duration of oxygen (hours)was 27.21±26.20 in the saline group which was significantly less than 10.67 ± 7.91 p value .003. This corresponds to a large effect size of 0.85. However, there were no significant differences in mean CSS score at 24 hours p value 0.921 or CSS score 6 and above at 24 hours p value 0.939. (Table 3)

Table 3: The measure of efficacy between two study groups

	Groups		
Variable	Saline n=38	Hypertonic n=26	P value
LOS (hours)	75.53±43.87	45.92 ±12.19	000 (a)
Oxygen (c) duration (hours)	27.21± 26.20	10.67± 7.91	0.03 (a)
CSS 24 hours	5.42 ±2.92	4.50±2.88	.921
CSS category 24 hours			0.939(b)
Normal	6 15.8%	4 15.4%	
Mild (1-5)	13 34.2%	10 38.5%	
6 and above	19 50%	12 46.2%	

LOS: length of hospital stay.
a) continuous variable independent T-test categorical variable
b) Chi-square test
© 44 patients needed oxygen of which 29 were in saline and 15 were in a hypertonic group

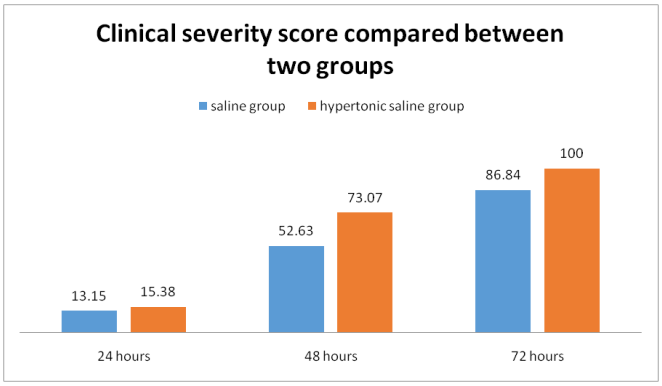

Figure 1: Proportions (percentage within group total) of subjects who were CSS score 0 at treatment intervals.

Figure 1 shows the proportion of subjects (percentage within the group) who became normal (score 0) at subsequent treatment intervals. The data showed at 72

hours of 48 hours of treatment 73.07% of subjects in hypertonic saline and 52.63% in the normal saline group had CSS scores of 0. In the hypertonic group, all 26 patients had a CSS score of 0, while 5 patients in the saline group didn't achieve a CSS score of 0 at 72 hours. Of these, two patients were still CSS score category 6 and above and three patients were CSS category mild (score 1-5). All the patients were discharged after successful treatment although two patients in the saline group left against medical advice.

4. Discussion

Bronchiolitis is a common infection of small airways in young children less than 2 years old in the winter season with a significant number of admissions in Pediatric wards.[12,13] It is diagnosed usually on clinical assessment of children. Supportive care is the standard treatment for acute bronchiolitis due to its self-limiting nature and good outcome.[14] This is the first reported study in the Holy Family Hospital, Rawalpindi comparing nebulized Hypertonic saline (HS) versus nebulized Normal Saline (NS).

Our study demonstrates the advantage of nebulized therapy with HS over NS in terms of length of hospital stay and decreased oxygen requirement but no advantage on clinical severity score. In our study, the mean age of children involved was 7.6 (± 3.75) months with a range from 01 months to 18 months of age. To minimize any confounding factors, strict inclusion criteria were applied. The randomization process of patients and the blinding of researchers minimized selection bias. Clinical Severity Score was selected for our study design due to its easy scoring method and applicability. There was no statistical difference in demographic characteristics for both groups. The children enrolled in the study, fulfilled the definition of bronchiolitis, including clinical severity score within mild to moderate. These patients received 6 hourly nebulizations (either in group 1 or group 2) and the clinical score was recorded. The patients' monitoring was stopped as they fulfilled the termination criteria of the study.

In one study done in 2020 by Awang N, et al, they did a randomized controlled trial study. They added nebulized salbutamol with hypertonic saline and normal saline. Their study showed that there is no difference in terms of length of hospital stay and the clinical severity score improvement in both groups.[15] In another study done in 2020 by Hsieh CW, et al, they did a randomised control trial to explore the efficacy of hypertonic saline over normal saline. They concluded that hypertonic saline is effective in decreasing the length of stay and symptom severity as compared to another group receiving normal saline.[16]

A latest study published in 2023 by Zhang L, et al also assessed the efficacy of hypertonic saline in acute bronchiolitis. Their results are close to our study in terms that hypertonic saline modestly reduced the length of stay in infants with a slight improvement in clinical severity score. [17] A local study done in Multan in 2019, they also compared the efficacy of hypertonic saline over normal saline and found out no significant outcome in length of hospital stay in both groups.[18] In another systematic review and meta-analysis done by Pereira, et al they combined hypertonic saline with bronchodilators and the results showed shortened hospital stay and reduction of clinical severity score effectiveness.[19] In another randomized control trial done by Angoulvant, they compared the groups with hypertonic saline and normal saline and found that the use of hypertonic saline does not reduce the length of hospital admission in children.[20]

Limitations: The majority of our patients with bronchiolitis may receive a bronchodilator in an emergency before enrollment in the study. These patients may have mild to moderate illness based on the clinical severity score. Other significant factors that may contribute to the number of subjects in the recruitment of the study are due to the first provisional diagnosis on admission. If the impression is related to viral wheeze or pneumonia, the patients will not be recruited in this study. The small sample size is also another limitation.

5. Conclusion

Nebulization with hypertonic saline reduces oxygen requirement and benefits in reducing the length of hospital stay.

CONFLICTS OF INTEREST- None

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Contributions:
U.A, A.A, N.Z, A.F, S.Y, S.F - Conception of study
U.A, S.F - Experimentation/Study Conduction
U.A, A.A, N.Z, A.F, - Analysis/Interpretation/Discussion
U.A, A.A, N.Z, A.F, S.Y - Manuscript Writing

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U.A, A.A, S.Y, S.F - Facilitation and Material analysis

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