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Paediatrics Section

Salbutamol Nebulisation in Normal Saline versus Salbutamol Nebulisation in Hypertonic Saline (3%) in Children with Acute Asthma Exacerbation: An Open-labelled Randomised Controlled Trial

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ABSTRACT

Introduction: Asthma has a significant impact and is the leading cause of morbidity and mortality in children. Salbutamol has been the cornerstone of treatment for bronchial constriction in asthma. Conventionally, salbutamol is diluted in Normal Saline Solution (NSS) and used for nebulisation. Studies conducted on bronchiolitis have demonstrated that using hypertonic saline instead of Normal Saline (NS) can decrease the viscosity of secretions and thus clear the airways.

Aim: To compare the efficacy of salbutamol nebulisation in NS versus salbutamol nebulisation in hypertonic (3%) saline in children with acute asthma exacerbation.

Materials and Methods: This open-labelled randomised controlled trial was conducted in the Department of Paediatrics at Pandit BD Sharma Post Graduate Institute of Medical Science, Rohtak, Haryana, India. The study involved 200 children between the ages of 5 and 14 years who presented with acute asthma exacerbation at the same institute from November 2022 to October 2023. A scoring system, the Becker asthma severity score, was used to classify the children as having mild/moderate or acute severe asthma. The study sample was divided into two groups: Group A (Control group: Salbutamol nebulised with NS) and Group B {(Study group: Salbutamol nebulised with Hypertonic Saline (HS))}. Both groups were compared in terms of improvement in symptoms using the Paediatrics Respiratory Assessment Measure (PRAM) score, duration of hospital stay and the requirement for admission to the Paediatrics Intensive Care Unit (PICU). An unpaired t-test and Chi-square test were performed, and the p-value was calculated, with a significance level set at <0.05.

Results: In the present study, both groups were comparable in terms of age, gender (p=0.039), socioeconomic status, and residence. The Paediatric Respiratory Assessment Measure (PRAM) score was comparable in the hypertonic saline and NS groups at the beginning. However, the PRAM score was significantly lower in the hypertonic saline group compared to the NS group at 20 minutes (6.12±1.26 versus 6.84±1.13), 40 minutes (4.85±0.83 versus 5.14±1.00), and 60 minutes (3.14±0.64 versus 3.87±0.65). The PICU admission rate was significantly lower in the hypertonic saline group (24.6%) compared to the NS group (75.4%). A higher number of patients in the hypertonic saline group were discharged within 24 hours compared to the NS group.

Conclusion: The 3% hypertonic saline group, in comparison with the 0.9% NS group, showed greater efficacy in relieving symptoms and reducing the length of hospital stay in children with acute exacerbation of asthma.

Keywords: Bronchodilator, Paediatrics respiratory infection, Reactive airway disease

INTRODUCTION

Asthma is a worldwide condition that affects individuals of different ages and geographical locations. Total 10% of the 300 million people suffering from asthma globally reside in India [1]. Asthma often begins in childhood, with many cases diagnosed before the age of five years [2]. It has a significant impact and is a leading cause of morbidity and mortality in children. The percentage of children and adolescents with a clinical diagnosis of asthma has increased from 9% to 17% over the past two to three decades [3]. It is one of the most common chronic respiratory diseases, frequently resulting in emergency room visits and repeated hospitalisations.

For more than 60 years, beta-2 agonists have been the cornerstone of treatment for bronchial constriction in acute asthma. Salbutamol is commonly used with NSS for nebulisation, creating a total salbutamol solution of 3-5 mL. Inhaled Hypertonic Saline Solution (HSS) has been increasingly used in recent decades for asthma. Its mucolytic properties make it an effective agent for decreasing secretion viscosity in several respiratory diseases and are also used to induce sputum for certain diagnostic tests [4].

The HSS exerts osmotic effects on the airway surface layer, increasing the volume of the periciliary layer phase and consequently improving mucociliary clearance. The use of HSS in nebulisation solutions has been found to diminish mucus viscosity when managing children with cystic fibrosis, non cystic fibrosis bronchiectasis, bronchiolitis, chronic bronchitis, and ciliary dyskinesia [5]. The HSS has also been extensively evaluated in acute bronchiolitis, where it demonstrated a positive influence on both hospitalisation rates and the length of stay in children with bronchiolitis [6].

Previously published literature regarding the use of hypertonic saline as an adjuvant solution in nebulisation has primarily focused on its use in acute bronchiolitis [7-9]. This is the first study of its kind to use hypertonic saline instead of NS as a nebulisation adjuvant, assessing its role in relieving the viscosity of secretions in bronchial airways. In the present study, a comparison of the nebulisation solutions of salbutamol with the conventionally used NS and hypertonic saline was conducted to assess clinical outcomes for children presenting to the Paediatrics Emergency Department with acute severe asthma episodes.

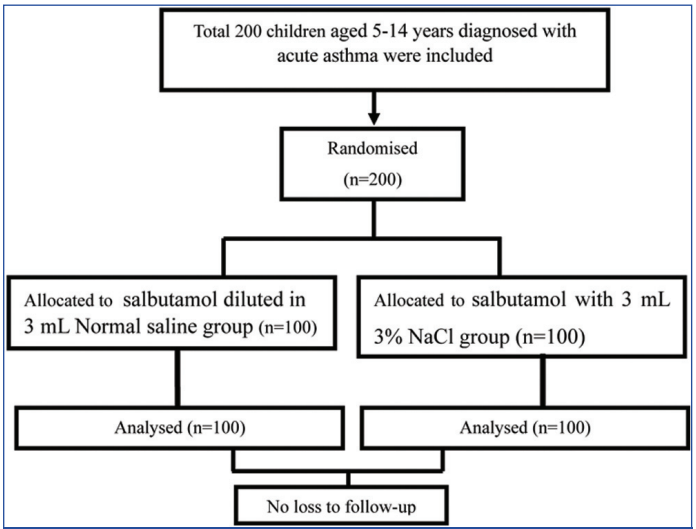
MATERIALS AND METHODS

The present open-labelled randomised controlled trial was conducted in the Department of Paediatrics at the Postgraduate Institute of Medical Sciences in Rohtak, Haryana, India, from November 2022 to October 2023. The study commenced after obtaining approval from the Institutional Ethics Committee (IBC No. BREC/22/TH/Ped/012) and Clinical Trial Registration (CTRI No. CTRI/2023/07/055475).

Inclusion criteria: Children aged 5-14 years diagnosed with acute asthma exacerbation, consistent with moderate to severe severity according to the Becker Asthma Severity Score, were included in the study. The Becker Asthma Severity Score typically includes parameters such as respiratory rate, accessory muscle use, wheezing, oxygen saturation, and the inability to speak in sentences. Each parameter is assigned a score, and the total score determines the severity of the exacerbation. A score greater than 4 is considered moderate status asthmatic, while a score greater than 7 indicates severe acute asthma [10].

Exclusion criteria: Children with abnormal airway development, congenital respiratory diseases, or known histories of heart, liver, neurological, or kidney diseases were excluded from the study. Additionally, children with evidence of pneumonia as per World Health Organisation (WHO) ARI classification or those with a history of tachyarrhythmia and bradyarrhythmia were also excluded [11].

Sample size calculation: In present study, a total of 200 patients were enrolled by calculating the appropriate sample size and accounting for attrition in the study [Table/Fig-1]. Therefore, the final sample size was 100 in each group. The sample size was determined using a convenience sampling technique. This number was based on the approximate number of patients visiting the Paediatrics Emergency Department during the stipulated time of the thesis period.



[Table/Fig-1]: Consort type diagram of flow of participant.

Study Procedure

The attendants of the children were informed about the study, and written informed consent was obtained from them. After taking a thorough history, each child underwent detailed clinical examinations. A scoring system, the Becker Asthma Severity Score, was used to classify the children as having mild/moderate or acute severe asthma. Variable size block randomisation (2, 4, or 6) was performed using a computer-generated randomisation sequence by a person not involved in the study. The study sample was randomised into two groups: Group A was nebulised with salbutamol diluted in 3 mL of NS, while patients in Group B were nebulised with salbutamol diluted in 3 mL of 3% NaCl (HS) (duration of nebulisation: 10-15 minutes). The duration of illness, frequency of symptoms during the day and night, respiratory rate, heart rate, oxygen saturation, and PRAM score were measured at the beginning of nebulisation and then at 20, 40, and 60 minutes after nebulisation. Both groups were compared in terms of improvement in symptoms using the PRAM score, duration of hospital stay, and the requirement for admission to the PICU. The PRAM score is a clinical tool used to assess the severity of asthma exacerbations in children. It helps healthcare providers determine the need for interventions such as bronchodilators and corticosteroids. It evaluates five parameters: suprasternal retraction, scalene retraction, air entry, wheezing, and oxygen saturation. The total PRAM score is calculated by summing the scores for each parameter, with a maximum score of 12 [12].

STATISTICAL ANALYSIS

The presentation of categorical variables was done in the form of numbers and percentages. On the other hand, the quantitative data were presented as means±SD and as medians with 25th and 75th percentiles (interquartile range). The following statistical tests were applied for the results: the comparison of variables that were quantitative in nature was analysed using the independent t-test, while the comparison of variables that were qualitative in nature was analysed using the Chi-square test. If any cell had an expected value of less than 5, then Fisher's-exact test was used. The Shapiro-Wilk test was used to test the normality of the data. Data entry was performed using a Microsoft Excel spreadsheet, and the final analysis was conducted using the Statistical Package for Social Sciences (SPSS) software, IBM Corporation, Chicago, USA, version 25.0 (trial version). For statistical significance, a p-value of less than 0.05 was considered statistically significant.

RESULTS

There was no significant difference between Group A and Group B in terms of age, while the difference was statistically significant (p=0.039) for gender in both groups [Table/Fig-2].

Parameters		Normal Saline (NS) (Group A) n (%)	Hypertonic Saline (HS) (Group B) n (%)	Total N (%)	p-value
Age group (years)	5-7	30 (15%)	30 (15%)	60 (30%)	1.0
	>7-11	34 (17%)	34 (17%)	68 (34%)	
	>11-14	36 (18%)	36 (18%)	72 (36%)	
Gender	Female	29 (40.3%)	43 (59.7%)	72 (36%)	0.039
	Male	71 (55.5%)	57 (44.5%)	128 (64%)	
	Total	100 (50%)	100 50%)	200 (100%)	

[Table/Fig-2]: Demographic Profile of study subjects.

The HSS group and NSS group were comparable in terms of the parameter of duration of illness (3.89±1.26 versus 4.03±1.21 days, respectively). Group A and Group B were comparable in terms of the parameters of frequency of day symptoms (3.43±0.73 versus 3.70±1.04, respectively) and frequency of night symptoms (5.73±0.89 versus 5.85±0.83, respectively) [Table/Fig-3].

Parameters	Treatment group		Total	p-value
	Group A Mean±SD	Group B Mean±SD	Mean±SD	
Duration of illness (days)	4.03±1.21	3.89±1.26	3.96±1.24	0.323
Frequency of symptom during day	3.70±1.04	3.43±0.73	3.57±0.91	0.055
Frequency of symptom during night	5.85±0.83	5.73±0.89	5.79±0.86	0.733

[Table/Fig-3]: Comparison of duration of illness and frequency of symptoms at day and night in the two groups.

The Becker Asthma Severity Categories, which included 28 children with moderate exacerbation, 29 children with severe exacerbation, and 43 children with respiratory failure in each group has been depicted in [Table/Fig-4].

Parameters		Treatment group			p-value
		Group A	Group B	Total	
		n (%)	n (%)	N (%)	
Becker Asthma Severity Category	Moderate exacerbation	28 (50%)	28 (50%)	56 (28%)	1.00
	Respiratory failure	43 (50%)	43 (50%)	86 (43%)	
	Severe exacerbation	29 (50%)	29 (50%)	58 (29%)	
	Total	100 (50%)	100 (50%)	200 (100%)	

[Table/Fig-4]: Becker Asthma Severity Category at the time of admission.

The oxygen saturation was significantly higher in Group B compared to Group A at 60 minutes (93.65±4.18 versus 92.53±3.67, respectively). The PRAM scores were significantly lower in Group B compared to Group A at 20 minutes (6.12±1.26 versus 6.84±1.13, respectively), 40 minutes (4.85±0.83 versus 5.14±1.00, respectively), and 60 minutes (3.14±0.64 versus 3.87±0.65, respectively) has been depicted in [Table/Fig-5].

Parameters	Treatment group		Total	p-value
	Group A	Group B		
	Mean±SD	Mean±SD	Mean±SD	
Oxygen saturation at beginning (%)	81.11±13.68	80.23±14.63	80.67±14.14	0.402
Oxygen saturation at 20 minutes	84.34±10.38	84.80±10.69	84.57±10.51	0.259
Oxygen saturation at 40 minutes	88.01±7.20	89.07±7.12	88.54±7.16	0.057
Oxygen saturation at 60 minutes	92.53±3.67	93.65±4.18	93.09±3.96	0.014
PRAM score at beginning	8.70±1.57	8.71±1.58	8.70±1.57	0.956
PRAM score at 20 minutes	6.84±1.13	6.12±1.26	6.48±1.25	<0.001
PRAM score at 40 minutes	5.14±1.00	4.85±0.83	4.99±0.93	0.028
PRAM score at 60 minutes	3.87±0.65	3.14±0.64	3.50±0.74	<0.001

[Table/Fig-5]: Comparison of oxygen saturation and PRAM score at 20, 40 and 60 minutes for treatment groups.

Out of 100 patients in Group B, only 14 patients had PICU admissions. Out of 100 patients in Group A, 43 patients had PICU admissions, and the application of the t-test showed that the differences were statistically significant, indicating that Group A had significantly higher PICU admissions. Out of 100 patients in Group B, 40 patients were discharged within 24 hours, 31 patients were discharged within 24-72 hours, and 29 patients were discharged after 72 hours. Out of 100 patients in Group A, 28 patients were discharged within 24 hours, 43 patients were discharged within 24-72 hours, and 29 patients were discharged after 72 hours. The application of the t-test showed that the differences were not statistically significant, indicating that the two groups were comparable in terms of length of hospital stay has been depicted in [Table/Fig-6].

Parameters		Treatment group			p-value
		Group A	Group B	Total	
		n (%)	n (%)	N (%)	
PICU admission	No	57 (39.9%)	86 (60.1%)	143 (71.5%)	<0.001
	Yes	43 (75.4%)	14 (24.6%)	57 (28.5%)	
	Total	100 (50%)	100 (50%)	200 (100%)	
Length of hospital stay (hours)	<24 hours	28 (41.17%)	40 (58.82%)	68 (34%)	0.95
	24-72 hours	43 (58.10%)	31 (41.89%)	74 (37%)	
	>72 hours	29 (50%)	29 (50%)	58 (29%)	
	Total	100 (50%)	100 (50%)	200 (100%)	

[Table/Fig-6]: Comparison of PICU admission and length of hospital stays in Group A and Group B.

DISCUSSION

The present study was conducted on 200 children aged 5-14 years with acute asthma exacerbation in the Department of Paediatrics, Postgraduate Institute of Medical Sciences, Rohtak, Haryana to compare salbutamol nebulisation in NS versus salbutamol nebulisation in hypertonic saline (3%) in children with acute asthma exacerbation.

Upon comparing the demographic parameters in Group A and Group B, it was found that both groups were comparable in terms of age and sex. The PRAM score is used to assess the severity of asthma exacerbation [13]. The PRAM score was comparable in the hypertonic saline and NS groups at the beginning. However, the PRAM score was significantly lower in the hypertonic saline group compared to the NS group-at 20 minutes, 40 minutes, and 60 minutes. These results indicate that salbutamol nebulised with HSS is more effective in the treatment of bronchial asthma compared to salbutamol nebulised with NSS.

Similarly, Teper A et al., also found that the efficacy of nebulised albuterol administered with a hypertonic solution of 3% NaCl (3% HSS) was higher compared to an isotonic solution of 0.9% NaCl (NSS) in mild or moderate obstructive asthmatic children, which is consistent with the results of the present study [14].

The HSS has also been extensively evaluated in acute bronchiolitis. A meta-analysis in bronchiolitis showed that HSS has a positive influence on both hospitalisation rates and the length of stay [15]. The action of HSS is mainly attributed to a decrease in respiratory epithelium oedema and work of breathing. The use of salbutamol with HSS as a diluent has not yet been sufficiently evaluated in asthma. Research has demonstrated the ability of HSS to reduce IL-4 levels, suggesting that it may have a mild anti-inflammatory effect [16].

Ater D et al., in their study on wheezy preschool children with and without risk factors for asthma presenting in an emergency department with obstructive symptoms found that the administration of albuterol nebulised with 5% HSS resulted in a lower rate of hospitalisation and a shorter length of stay compared to NSS [17]. Furthermore, Forouzan A et al., in their study of adult asthmatic patients found superior efficacy of albuterol nebulisation in HSS compared to albuterol nebulisation in NSS (3% HSS achieved an FEV1 BDR of 33.6% versus 22.7% with albuterol in NSS), which is consistent with the results of the present study [18].

The mechanisms that explain the enhanced bronchodilator effect of HSS in salbutamol in asthma are unclear. The inflammation, mucosal hypersecretion, and eventual cell desquamation present in the lower airways of asthmatic subjects with bronchial obstruction favor dehydration. A reduction in the volume of the airway surface layer and a decrease in mucociliary transport leads to the development of mucus plugs in the airways of small caliber [19].

In the present study, the PICU admission rate was significantly lower in Group B compared to Group A, reflecting the better bronchodilator effect of HSS compared to NSS in bronchial asthma. The indication for PICU admission is a lack of response to bronchodilators, anticholinergics, and steroid use, where further treatments in the algorithm for managing acute severe asthma, such as MgSO4 infusions, are given in ICU settings. In the index study, this was found to be statistically significant in the NSS group.

In the present study, the length of stay was shorter in Group B compared to Group A in bronchial asthma, as a higher number of patients were discharged within 24 hours, although the difference between the two groups was not statistically significant. Tal G et al., found that substituting hypertonic saline for NSS in the inhalation

Authors name	Place/year	Sample size	Type of study	Intervention	Result	Conclusion
Teper A et al., [14]	2021	N=50	A prospective, experimental, double-blind, randomised clinical study	Bronchodilator responses to salbutamol nebulised with 3% hypertonic saline in asthmatic children, compared to salbutamol nebulised with Normal Saline Solution (NSS)	Higher bronchodilator response to Forced Expiratory Volume (FEV1) in hypertonic saline than in NS. Maximum mid-expiratory flow was 130% and 69.8% for the 3%-HSS and NSS groups, respectively.	Albuterol produces a greater bronchodilator response when nebulised with 3%-HSS compared to the NSS in asthmatic children with mild or moderate bronchial obstruction.
Hossain RM et al., [7]	Bangladesh/2022	N=100	Randomised control trial	4 mL 3% hypertonic saline nebulisation versus 0.4 mL salbutamol respiratory solution nebulisation	The length of hospital stay was shorter in 3% hypertonic saline group. No side effects were observed.	3% hypertonic saline nebulisation significantly reduces clinical severity and length of hospital stay of children suffering from acute bronchiolitis in comparison to those treated by NS and salbutamol nebulisation.
The present study	PGIMS Rohtak/2023	N=200	Randomised control trial	Salbutamol nebulisation with NS versus hypertonic saline	PRAM Score was significantly lower in hypertonic saline group as compared to NS group.	Hypertonic saline showed more efficacies in relieving symptoms and reducing the length of hospital stay in children with acute exacerbation of asthma.

[Table/Fig-7]: Comparison of main parameters between previous published literature and our study [7,14].

mixture for delivering bronchodilators improved clinical scores and decreased hospitalisation rates in ambulatory children, resulting in lower PICU admissions, which is consistent with the results of the present study [20].

In most past studies, hypertonic saline was used as an inhalational challenge for cough provocation tests among stable asthmatic patients in outpatient respiratory clinics, while in the present study we evaluated the therapeutic efficacy of 3% hypertonic saline with higher inhalation time (20 min) and salbutamol with a higher dosage (2.5 mg) among children with acute asthma in the emergency department [21,22]. Furthermore, adherence to the therapeutic intervention was high, and no serious adverse events were recorded in the case of HSS. These findings suggest that the inhalation of 3% hypertonic saline as part of the management of acute asthma is both well tolerated and feasible in clinical practice. Comparison of main parameters between previous published literature and present study has been depicted in [Table/Fig-7] [7,14].

Limitation(s)

The study was conducted at a single centre, which does not reflect the overall scenario in India. Therefore, the present study requires a large, multi-scale, multi-centre countrywide study for more authentic outcomes, the sample size was small, which precluded us from obtaining statistical significance regarding certain variables and the studied cases with moderate to severe acute exacerbation of asthma; therefore, the results may not be generalisable to mild cases of asthma.

CONCLUSION(S)

The study demonstrated that the PRAM score of both treatment groups of children studied decreased, and oxygen saturation in room air improved with treatment. However, the reduction was more significant in children who received 3% nebulised hypertonic saline compared to those who received 0.9% nebulised NS and salbutamol. The 3% HS group showed more efficacy in relieving symptoms and reducing the length of hospital stay in children with acute exacerbation of asthma compared to the 0.9% NS group. The bronchodilator effect produced by the nebulisation of salbutamol delivered in 3% HS is greater than that with NS in asthmatic children with severe bronchial obstruction. Our results indicated the short-term efficacy of 3% HS in acute asthma attacks, and the inhalation of 3% HS as part of the management of acute asthma is both well tolerated and feasible in clinical practice. Therefore, it may be used as a supplemental drug along with salbutamol in patients with acute asthma attacks admitted to the emergency department.

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