International Journal of Contemporary Pediatrics
Pamecha P et al. Int J Contemp Pediatr. 2021 Jul;8(7):1176-1182
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20212468

Original Research Article

A randomized controlled trial of nebulized epinephrine versus nebulized hypertonic saline in infants with acute bronchiolitis

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Received: 08 April 2021
Revised: 02 June 2021
Accepted: 03 June 2021

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ABSTRACT

Background: Acute Bronchiolitis is an infection of the lower respiratory tract, most frequently caused by the respiratory syncytial virus. It is one of the most common cause of hospital admission for respiratory tract illnesses in infants. This is a double blinded randomized controlled trial, conducted to compare the therapeutic efficacy of nebulized epinephrine versus nebulized hypertonic saline in infants with acute bronchiolitis.
Methods: It was a double blinded randomized controlled trial conducted over a period of 18 months (January 2019-June 2020) in infants aged 2 months to 1 year diagnosed with acute bronchiolitis. All eligible patients were randomly assigned to one of two groups: Group I received inhalation of Epinephrine; Group II received inhalation of Hypertonic (3%) Saline. Patients in each group received four treatments on each day of hospitalization, delivered at 6 hourly intervals. Monitoring parameters for improvement or worsening of the condition were measured and recorded on admission and then at 24 hourly intervals using the clinical score described by Wang, et al for the first three days of treatment.
Results: Among the infants treated with hypertonic saline, there was a significant decrease in the post inhalation respiratory score on day 2 and day 3 as compared to the infants treated with epinephrine. There was a significant difference in duration of hospitalization between the two groups as duration of hospitalization in infants was less in hypertonic saline group as compared to the epinephrine group. Hypertonic saline also showed significantly lesser side effects post inhalation when compared to epinephrine. The difference was statistically significant with $p<0.0001$.
Conclusions: The study concluded that the use of nebulized hypertonic saline in infants aged 2 months to 12 months, provides evidence for its role as an efficient treatment modality in the treatment of acute bronchiolitis. The study also found that nebulized epinephrine had more side effects associated with it.

Keywords: Acute bronchiolitis, Epinephrine, Hypertonic saline

INTRODUCTION

Acute bronchiolitis, primarily an infection of the lower respiratory tract, is most frequently caused by the respiratory syncytial virus. It is one of the most common cause of hospital admission for respiratory tract illnesses in infants less than 2 years of age. Peak incidence occurs before 6 months of age in 70-80 percent of cases. Globally, the World Health Organization (WHO 2009) estimates that RSV causes 64 million infections and 1,60,000 deaths annually.[1] Respiratory syncytial virus is the most common cause of childhood acute lower respiratory tract infections and a major cause of admission to hospital as a result of severe acute lower respiratory tract infections with 99% of the respiratory syncytial virus-related deaths taking place among resource-limited countries like India.[1]

Acute bronchiolitis is an infection of the bronchiolar epithelium, characterized by necrosis and sloughing of epithelial cells, increased secretion of mucus, edema and

peribronchiolar mononuclear infiltration leading to obstruction of flow in the large and small airways ultimately leading to hyperinflation, wheezing, and/or atelectasis. Bronchiolitis is more common in males, in children who have not been breastfed, and in those who live in crowded conditions. Risk is higher for infants with young mothers or mothers who smoked during pregnancy, prematurity, chronic lung disease, congenital heart disease and immunosuppression.[1,2]

Initially, the infant develops a mild upper respiratory tract infection with sneezing and clear rhinorrhea, which may be accompanied by diminished appetite and fever of 38.5-39°C (101-102°F), although the temperature can range from subnormal to markedly elevated. Gradually, infant becomes tachypneic which can interfere with feeding, respiratory distress ensues, with paroxysmal wheezy cough, dyspnea, and irritability. Apnea may be more prominent than wheezing early in the course of the disease, particularly with very young infants i.e. 2 months old or former premature infants. Hypoxemia is a consequence of ventilation–perfusion mismatch early in the course. With progression to severe obstructive disease and tiresome respiratory effort, hypercapnia can develop.[3]

In a previously healthy infant presenting with a 1st-time wheezing episode during a community outbreak, the diagnosis of acute bronchiolitis is purely clinical.[3] Since one of the physical signs of the disease is wheezing, physicians have treated the disease with steroids and beta agonists. However, these treatments as well as ribavirin, the only known anti respiratory syncytial virus agent, are considered controversial and the mainstay of treatment still remains hydration and supplemental oxygen.[1,2,4-10]

Treatment with nebulized hypertonic saline and epinephrine have found to decrease severity of symptoms in infants with acute viral bronchiolitis as well as shorten the duration of hospitalization. It is simple, seemingly efficient, cost effective and has an excellent safety profile.[11] Hence, more research is warranted for further confirmation and expansion of data to clarify this potential treatment modality.

The objectives of this study are to compare therapeutic efficacy of nebulized epinephrine versus nebulized hypertonic saline in infants with acute bronchiolitis based on clinical scoring and average length of hospital stay, to comparatively assess respiratory parameters (wheeze, oxygen saturation, respiratory rate and chest retraction) in both groups and to compare side effects of the involved drugs in both groups.

METHODS

tudy. It was a double blinded randomized controlled trial conducted over a period of 18 months (January 2019 to June 2020) in infants aged 2 months to 1 year diagnosed with acute bronchiolitis at Department of Pediatrics, Geetanjali Medical College and Hospital. Udaipur. The study was conducted after the approval of institutional ethical committee. Details of the study were explained to the parents of each child and written informed consent was obtained voluntarily from at least one each of the parent before child entered the study. Infants with a chronological age of 2 months to 12 months, a clinical diagnosis of mild to moderate bronchiolitis (defined as the first episode of wheezing and clinical symptoms of a viral respiratory infection), an initial oxygen saturation of 85% or more but 96% or less on arrival to the Pediatric Ward, and if their initial Wang respiratory score12 was 3 or higher were included in the study.

A total of 146 infants were enrolled for the study. Patients were randomized into two groups by using chit method for a comparable distribution in each group. Group I received inhalation of 3 ml epinephrine; Group II received inhalation of 3 ml hypertonic (3%) saline. 3 mL aliquots of epinephrine and 3 mL aliquots of a second, indistinguishable solution of 3% hypertonic saline was prepared. The solutions were stored in identical syringes, labelled only by a code number, and placed in the research cupboard within the Pediatric ward. The combination code of the therapeutic package (epinephrine versus 3% hypertonic saline) was not available to the patient's parent(s) or treating medical staff. The randomization list was concealed until completion of the study.

Patients in each group received four treatments of the allotted drug per day, delivered at 6 hourly intervals. Infants in either group received doses of treatment by a conventional jet nebulizer with continuous flow of 100% oxygen at 6 L/min through a well fitted face mask. Nebulization was continued till the nebulization chamber was empty. Patients were examined by investigator at the study entry and every day. Monitoring parameters for improvement or worsening of the condition were measured and recorded on admission and then at 24 hourly intervals for the first three days of treatment using the clinical score described by Wang et al.[12]

The 4-item Wang respiratory score consists of respiratory rate, wheezing, chest retraction and general condition (Table 1) and each clinical sign is scored from zero to 3 as per its severity except for the general condition, which is scored zero for normal and 3 for irritability or lethargy. The possible total score ranges from 0–12. The respiratory rate was determined by counting the respiration for 30 seconds.[12]

Pediatric ward physicians were free to withdraw patients from the study or to use other interventions if deemed clinically necessary. Adverse effects of the drugs were recorded in both the groups. Patients in each group received treatments on each day of hospitalization, delivered at 6 hourly intervals, until the patient was ready for discharge. Discharge criteria included feeding well orally, no need for intravenous fluids and supplemental oxygen, clinical severity score of ≤3, absence of accessory

muscle use or tachypnea and oxygen saturation >96% on room air.

Statistical analysis

Data was entered in MS Excel software and analyzed using IBM Statistical package for social sciences (SPSS) statistical software version 2.1. Descriptive data is presented as mean standard deviation, proportion and frequency in contingency table. Categorical data was analyzed using Chi Square test, Mc Nemar's test. Quantitative data was analyzed using Student's-t test (Paired/Unpaired). Correlation analysis was done using Pearson's Correlation test. P<0.05 was concluded to be statistically significant.

RESULTS

Total 146 infants of either gender, aged 2 months to 1 year were enrolled. All were randomized into two groups (72 in each) to receive either of the drugs to be used in the study. Among the 73 infants in hypertonic saline group, 5 (6.8%) infants belong to the age group 2-4 months, 54 (74%) infants belong to the age group 5-7 months, 11 (15.1%) infants belong to the age group 8-10 months and 3 (4.1%) infants belong to the age group >11 months.

Table 1: Clinical signs and score of the Wang respiratory score.[12]

Score	Respiratory rate	Wheezing	Retraction	General condition
0	<30	None	None	Normal
1	30-45	Terminal expiration or only with stethoscope	Intercostal recession	
2	46-60	Entire expiration or audible on expiration without stethoscope	Trachea-sternal recession	
3	>60	Inspiration and expiration without stethoscope	Severe	Irritable/lethargic/poor feeding

Table 2: Demographic profile of all the children in both the groups.

Age (months)	HS group		EP group	
	N	**%**	**N**	**%**
2-4	5	6.8	4	5.5
5-7	54	74.0	47	64.4
8-10	11	15.1	18	24.7
≥11	3	4.1	4	5.5
Total	73	100	73	100
Mean ± SD	6.6±1.6		7.0±1.9	
Gender	**HS group**		**EP group**	
	N		**%**	**N**	**%**
Male	37		50.68	45	61.64
Female	36		49.32	28	38.36
Total	73		100	73	100

Table 3: Distribution of infants as per Wang respiratory score post inhalation.[12]

Respiratory rate scoring	HS group		EP group		P value
	Mean	**SD**	**Mean**	**SD**	
Day-1	2.5	0.5	2.41	0.50	0.2786
Day-2	1.6	0.6	2.00	0.44	<0.0001
Day-3	1.0	0.2	1.66	0.53	<0.0001
Wheezing	**HS group**	**EP group**	**P-value**		
	Mean	SD	Mean	SD	
Day-1	1.37	0.74	1.51	0.53	0.1909
Day-2	0.71	0.63	1.1	0.3	<0.0001
Day-3	0.07	0.25	0.2	0.4	0.0199
Chest retractions	**HS group**	**EP group**	**P value**		
	Mean	SD	Mean	SD	
Day-1	0.75	0.85	0.84	0.94	0.5450
Day-2	0.33	0.47	0.55	0.67	0.0231
Day-3	0.00	0.00	0.29	0.46	-

Continued.

Respiratory rate scoring	HS group		EP group		P value
	Mean	SD	Mean	SD	
General condition	**HS group**	**EP group**	**P value**		
	Mean	SD	Mean	SD	
Day-1	0.66	1.25	0.70	1.28	0.8488
Day-2	0.00	0.00	0.00	0.00	-
Day-3	0.00	0.00	0.00	0.00	-

Table 4: Distribution of infants according to duration of hospitalization and as preside effects of the administered therapy.

Duration of hospitalization	HS Group		EP Group		P value		
	N	%	N	%			
1-5 days	55	75.3	34	46.6	0.0004		
6-10 days	18	24.7	38	52.1	0.0010		
11-15 days	0	0	1	1.7	-		
Total	73	100	73	100			
Mean ± SD	5.1 ± 1.01		6.01 ± 1.45		0.6641		
Side effect	**HS group**		**EP group**		**P value**		
	N		**%**		**N**	**%**	
Tachycardia	9		12.3		27	37.0	<0.0001
Pallor	0		0.0		14	19.2	-
Tremors	0		0.0		7	9.6	-
Total	73		100.0		73	100.0	

Among the 73 infants in epinephrine group, 4 (5.5%) infants belong to the age group 2-4 months, 47 (64.4%) infants belong to the age group 5-7 months, 18 (24.7%) infants belong to the age group 8-10 months and 4 (5.5%) infants belong to the age group >11 months. The mean age in the hypertonic saline group was 6.6±1.6 months and in the epinephrine group it was 7.1±2.1. 37 (50.68%) infants were male and 36 (49.32%) infants were females. Among the 73 infants of epinephrine group 45 (61.64%) of infants were males and 28 (38.36%) infants were females.

The respiratory rate scoring at day-2 and day-3 decreased significantly ($p<0.0001$) in hypertonic saline group as compared to epinephrine group. Showing better outcome of hypertonic saline in decreasing respiratory rate when compared to epinephrine. Similarly, wheezing score also decreased significantly with $p<0.0001$ and p value 0.0199 on day 2 and day 3 respectively in hypertonic saline group as compared to epinephrine group. Showing better outcome of hypertonic saline in decreasing wheezing when compared to epinephrine. The difference in chest retractions between two group was significantly low in hypertonic saline group as compared to epinephrine group as $p<0.05$ at day-2. At day-3 there were no chest retractions in infants in hypertonic saline group. Both the drugs showed improvement in general condition of infants. There was no significant difference between the two groups as $p>0.05$ (Table 3).

There was a significant difference in duration of hospitalization between the two groups as duration of hospitalization in infants was less in hypertonic saline group as compared to the epinephrine group. In epinephrine group mostly, infants stayed in hospital for up to 10 days. But in hypertonic saline group mostly, infants stayed in hospital for up to 5 days (Table 4). In epinephrine group, 27 (37%) infants showed tachycardia, 14 (19.2%) infants showed pallor and 7 (9.6%) infants showed tremors after drug administration. Whereas in hypertonic saline group only 9 (12.3%) infants showed tachycardia. No infants in hypertonic saline group showed pallor and tremors. The difference was statistically significant with $p<0.0001$ (Table 4).

DISCUSSION

Acute bronchiolitis is the most common lower respiratory tract infection in infancy. It is an important cause of morbidity in infants and children. It is the most common cause of hospitalization due to acute lower respiratory tract infection (LRTI) in infants.[13] Globally, the World Health Organization (WHO 2009) estimates that RSV causes 64 million infections and 1,60,000 deaths annually.[1] Since one of the physical signs of the disease is wheezing, physicians have treated the disease with steroids and beta agonists. However, these treatments as well as ribavirin, the only known anti RSV agent, are considered controversial and the mainstay of treatment is still hydration and supplemental oxygen.[1,2,4-10]

Treatment with nebulized hypertonic saline and epinephrine has found to decrease symptoms in infants with acute viral bronchiolitis and shorten the average

length of hospital stay. It is simple, seemingly efficient, cost effective and has an excellent safety profile.[11]

In our study, the objectives were to compare therapeutic efficacy of nebulized epinephrine versus nebulized hypertonic saline in infants with acute bronchiolitis based on clinical scoring and average length of hospital stay, to comparatively assess respiratory parameters (wheeze, oxygen saturation, respiratory rate and chest retraction) in both groups and to compare side effects of the involved drugs in both groups. The study was conducted in Department of Pediatrics at Geetanjali Medical college and Hospital, Udaipur.

Total 146 infants fulfilling the inclusion criteria were enrolled, both male and female from age 2 months to 1 year. Maximum number of children in the age group of 5 - 7 months were diagnosed with acute viral bronchiolitis in both the groups. Fjaerli reported that majority of children (75% of total admissions) were hospitalized within the first year of life with children less than six months of age being responsible for 45% of all admissions with a median age at hospitalization of 6 months in a population based retrospective study on "Hospitalizations for Respiratory Syncytial Virus bronchiolitis in Akershus, Norway, 1993-2000".[14] Hervás et al also reported in a study that among the infants hospitalized for bronchiolitis, 1,836/2,384 (77%) were under 6 months of age.[15] Similarly, Luo et al reported in a study that, among the 112 patients, 57 were enrolled in the hypertonic saline group, with an average age of 5.9±4.1 months and 55 were enrolled in the normal saline group, with an average age of 5.8±4.3 months.[2]

In our study which included 73 infants in the hypertonic saline group, bronchiolitis was more common in male infants (50.68%) than female infants (49.32%). Also, among the 73 infants of epinephrine group, bronchiolitis was more common in male infants (61.64%) than female infants (38.36%). The results were similar to the previous studies conducted by Nagayama et al and Boezen et al.[16,17] Both studies showed increased susceptibility of bronchiolitis in male infants. The possible reason for this increased susceptibility could be due to immunosuppressive effect of the male hormones.[18]

In our study which included 146 infants among which 73 were treated with hypertonic saline and 73 infants were treated with epinephrine. Infants were assessed on the basis of Wang respiratory score which includes respiratory rate, wheezing, chest retractions and general condition, for the first three days of treatment. Among the 73 infants treated with hypertonic saline, there was a significant decrease in the post inhalation respiratory score on day 2 and day 3 as compared to the infants treated with epinephrine. Similar results were found in the trials conducted by Luo et al, Mandelberg and Tal.[11,19,20] These studies also demonstrated a statistically significant lower mean post-inhalation score among infants treated with 3% saline inhalation compared to those treated with 0.9% saline inhalation in the first three days of treatment. These results may suggest that nebulized hypertonic saline is effective for acute bronchiolitis only when the treatment is given at multiple daily doses during a reasonable period of time. However, the optimal treatment regime of nebulized hypertonic saline in infants with viral bronchiolitis still need to be established by further studies.

Among the 73 infants treated with epinephrine, there was a decrease in the post exhalation respiratory score on day 2 and day 3 but as compared to the treatment with hypertonic saline, the scores remained higher. Similar results were reported in studies conducted by Patel et al and Bertrand in which no clinically significant difference in the primary outcome measure, length of stay, in infants treated with extended-use nebulized epinephrine compared with those who received either nebulized albuterol or placebo was found.[8,21] Although, these studies suggested that epinephrine may be useful in edema reduction, by the time infants present to medical care. The short-term benefits in respiratory rate, oxygen saturation, and clinical score that have been observed with epinephrine may be more of a reflection of the general stimulant properties of this medication, as opposed to a therapeutic pulmonary effect.

In our current study, there was a significant difference in duration of hospitalization between the two groups as duration of hospitalization in infants was less in hypertonic saline group as compared to the epinephrine group. In epinephrine group mostly, infants stayed in hospital for up to 10 days. But in hypertonic saline group mostly, infants stayed in hospital for up to 5 days. This data is in correlation with trials conducted by Luo et al, Mandelberg, Tal and Kuzik that, there was approximately a one-day reduction in the duration of hospitalization.[11,19,20,22] The pooled results from these four trials demonstrate that nebulized 3% saline could produce a reduction of 1.16 days in the mean length of hospital stay. Given the high prevalence of viral bronchiolitis in infants and the tremendous burden of this illness related to hospitalization, this reduction may be considered clinically relevant and may potentially have a positive economic impact for both the health system and the individual families. Whereas, studies conducted by Patel et al and Bertrand concluded that extended-use nebulized epinephrine did not significantly shorten the length of stay in infants with acute viral bronchiolitis.[8,21]

In the current study, in epinephrine group, 37% infants showed tachycardia, 19.2% infants showed pallor and 9.6% infants showed tremors after drug administration. These results were significantly higher than the hypertonic saline group in which only 12.3% infants showed tachycardia while no infants in the hypertonic saline group showed pallor or tremors. Results of the epinephrine group of the current study are in coherence with a study conducted by Ray et al in which it was reported that post inhalation, adrenaline showed a significant increase in heart rate.[23] Plint et al too conducted a study on administration of epinephrine in acute bronchiolitis in

which it was reported that post inhalation, 9.5% infants developed pallor and 1.9% infants developed tremors.[24] The side effects caused by epinephrine may be contributed to its chronotropic action on heart and it poses as a matter of concern. Infants in the current study showed a significantly greater incidence of these side effects as compared to the previous studies.

In our study, in the hypertonic saline group, post inhalation only 12.3% infants showed tachycardia while no infants developed pallor or tremors. Zhang et al conducted a study which included 276 infants receiving 3% saline in repeated doses and no significant adverse events were reported.[25] Similarly, trials conducted by Anil et al, Sarrel, Luo et al, Mandelberg and Tal reported no difference in heart rate, on any day of the treatment.[11,19,20,26,27] Our study reports an increased incidence of infants showing tachycardia post inhalation of hypertonic saline which might have been contributed by excessive crying/irritability of infants during the course of inhalation.

Limitations

Despite showing significant outcomes, findings of this study have to be seen in light of some limitations as this study has been conducted with a limited sample size. Hence, elaborate trials are needed for further expansion of data.

CONCLUSION

In the light of the above results and observations it was found that the use of nebulized hypertonic saline in infants aged 2 months to 12 months, provides evidence for its role as an efficient treatment modality in the treatment of acute bronchiolitis. The study also found that nebulized epinephrine had more side effects associated with it.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Pamecha P, Mandot S. A randomized controlled trial of nebulized epinephrine versus nebulized hypertonic saline in infants with acute bronchiolitis. Int J Contemp Pediatr 2021;8:1176-82.