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Comparative Study of Nebulized Hypertonic Saline (3%) Epinephrine and Normal Saline in the Management of Children with Acute Bronchiolitis

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ABSTRACT

BACKGROUND: Nebulized adrenaline is used as preferred treatment in addition to supportive care in bronchiolitis but it causes tachycardia. Nebulized 3% saline and normal saline are also used. Few studies compared these 3 in efficacy and safety.

MATERIAL AND METHODS-Observational analytical study including 90 Children divided in 3 groups, aged 2-24 months, presenting with bronchiolitis. Length of hospital stay and treatment failure at 24 hours were the primary outcomes .Clinical scoring system by Uyan *et al* was used. Group A received Epinephrine, Group B received HS and Group C received NS. Patients enrolled successively in three groups. Scores and heart rate were monitored at 24 hours. Increase in score of 2 or more (from admission score) or heart rate above 200 or 10% increase over baseline, considered as treatment failure

RESULTS: Baseline characters of patients in three groups were similar. CS scores at admission were 7.8 in group A, 7.4 in group B and 7.6 in group C. After 24 hours, percentage decrease in CS score after inhalation therapy was better for group A (70%) and B (64%) compared to group C (16%). Score worsened in 2 patients of group A 3 patients of group B and 5 patients of group C, while 3 patients of adrenaline group were excluded due to tachycardia. Length of hospital stay was lower in group A and B (57.1 AND 55.7) compared to group C (74.8)

CONCLUSION Nebulized 3% saline and adrenaline are comparable but more effective than normal saline. Adrenaline has side effects of tachycardia.

Keywords: Hypertonic saline; acute bronchiolitis, Nebulized.

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INTRODUCTION

Bronchiolitis is an inflammatory and potentially fibrosing condition of the lower respiratory tract of infants, resulting from inflammatory obstruction of small airways mainly the intralobular conducting and transitional small airways. It is characterized by tachypnoea, wheezing, fine crackles and air trapping. It is caused by viral lower respiratory tract infection (LRTI) most commonly caused by RSV. It is characterized by acute inflammation, edema and necrosis of epithelial cells lining small air-ways, increased mucus production, and bronchospasm.[1] In the majority of cases, it is a mild and self-limiting illness that can be managed on ambulatory basis with supportive care alone. Management mainly consists of educating parents or caregivers about adequate feeding and to report any deterioration (such as increasing difficulty in breathing, chest indrawing or problems with feeding) to an appropriate health care facility. Multiple intervention studies have been carried out to improve treatment of bronchiolitis. [2]

Some children are too breathless to feed and some require oxygen supplementation to maintain blood oxygen levels. These children may require hospitalization. Nebulised bronchodilators like Salbutamol, Ipravent and terbutaline have been used by some in treatment of bronchiolitis. A Cochrane meta-analysis has not found these drugs to be useful.[3] In spite of the lack of objective evidence for their usefulness, these drugs are used extensively. The outcome measure used in this Cochrane meta-analysis was duration of hospital stay rather than improvement in respiratory distress. Another Cochrane analysis looking for benefits in terms of respiratory distress and oxygen requirement in immediate post treatment period with bronchodilator therapy, found improvement.[4]

A Cochrane review of the use of Epinephrine found evidence that it was more effective when used in the outpatient setting but no evidence of benefit when used in inpatients when compared against either placebo or Salbutamol,[5] Epinephrine however has the disadvantage of increasing heart rate.[6] Nebulised hypertonic saline is a new modality of treatment that has recently been used in bronchiolitis. It has previously been studied in the context of cystic fibrosis. Like bronchiolitis, children with cystic fibrosis have viscid secretions and wheezing. The hypertonic saline helps to reduce viscosity of secretions. A Cochrane meta-analysis of its use in cystic fibrosis concluded that nebulised hypertonic saline improves mucociliary clearance immediately after administration and that it may have a long term beneficial effect.[7] Nebulised hypertonic saline may be beneficial in bronchiolitis also may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis. A systematic review published in Indian Pediatrics looking at hypertonic saline against placebo found significant reduction in duration of hospital stay in the hypertonic saline group in children with bronchiolitis.[8] It seems that nebulised hypertonic saline with bronchodilators is better than bronchodilators alone and that hypertonic saline is better than placebo, but there is no study comparing hypertonic saline directly against bronchodilators and normal saline. In our hospital standard therapy for children with severe disease is nebulised Epinephrine and therefore it was considered appropriate to study nebulised hypertonic saline and normal saline against nebulised Epinephrine in hospitalized patients.

MATERIAL AND METHODS

This present observational analytical study was conducted in the Department of Paediatrics, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak a tertiary care government sponsored teaching hospital. A total of 90 children aged between two months and two years, who presented with an episode of acute bronchiolitis and respiratory distress were included in the study. Diagnosis was typically made by history and clinical examination. Clinical scoring system described by Uyan *et al* [9] was used. Prior to the initiation of the study a clearance was obtained from the Institutional P.G. Board of Studies. A written informed consent was obtained from the parents of each subject at enrolment. An infant under two years of age who developed with Cough, Wheeze, Coryza, Tachypnea, Ronchi on auscultation, X ray finding s/o Bronchiolitis, Oxygen saturation <94% on room air, Clinical score of 4 or more on Uyan *et al* scoring system[9] included in the study.

Score	0	1	2	3
Breathe Rate (/min.)	< 30	30 – 45	46 – 60	> 60
Retractions	No	Only intercostals	Intercostals, subcostal & supraclavicular	Abdominal respiration accompanying
Nasal flaring during inspiration	**No**	Mild & rarely	Moderate to Severe & intermittently	Severe & continuously
Wheezing	No	Heard only with Stethoscope	Heard in both phases of respiration with Stethoscope	Heard in both phases of respiration without Stethoscope
General Status	Normal	Moderately uneasy & occasionally crying	Very uneasy, crying continuously	Lethargic

Clinical Scoring System by Uyan *et al* [9]

Score 4-8 = moderately ill; 9 or more = severely ill

Children with history of Chronic cardiopulmonary disease, Immunodeficiency, Past history of respiratory disease requiring nebulization, Critical illness at presentation, Use of systemic or nebulized bronchodilators in last 24 hours, Use of nebulised hypertonic saline in last 24 hours and Pneumonia excluded from the study. Criteria for discontinuation were worsening of clinical score; tachycardia :- heart rate going above 200/minute or a 10% increase over baseline and increase in clinical score of 2 or more (using admission score as baseline).

With regard to outcome, parameters assessed was (i) length of hospital stay or time taken to be ready for discharge (inpatients) and (ii) Treatment failure at 24 hours as primary outcome and (i) Rate of hospitalisation to I.P.D, (ii) Clinical severity scores,

(iii) Rate of readmission to hospital, (iv) Time for the resolution of symptoms/signs, (v) Duration of in-hospital oxygen supplementation and (vi) Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting, diarrhoea and acute urinary retention) for secondary outcome.

Methods:

Of the 90 patients enrolled in the study, 30 received nebulised Epinephrine [Group A], 30 got nebulised hypertonic saline [Group B] and 30 received normal saline [Group C]. Patients were enrolled on successive basis in either of three groups started with nebulised Epinephrine followed by next patient getting hypertonic saline and then the next patient being administered normal saline in that order. Group A children were treated with nebulised d-Epinephrine of (1:1000) concentration, 1 ml diluted in 2 ml normal saline every 6 hourly for first 24 hours and was monitored using the same scoring system. Heart rate during first 24 hours of therapy was tracked. Any child with increased clinical score of 2 or more (using admission score as baseline) or if heart rate went above 200/minute or if there was 10% increase over baseline, was considered as treatment failure. In case of failure, the drug was stopped and alternative measures instituted which was escalated up to ventilation. Group B children received nebulised hypertonic (3%) saline 3 ml every 6 hours. Clinical score and heart rate was monitored. Success and failures were measured by the same criteria as with Epinephrine. Group C children received nebulised normal (0.9%) saline 3 ml every 6 hours. Clinical score and heart rate was monitored. Success and failures were measured by the same criteria as with Epinephrine and hypertonic saline.

Statistical analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables presented as mean±SD and categorical variables presented as frequency and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test for two groups and for multi group comparisons Analysis of Variance (ANOVA) used. Nominal categorical data between the groups was compared using Chi-square test. A two sided p value less than 0.05 was considered statistically significant.

RESULTS

In the present study, majority of children were upto 6 months of age in all the groups i.e. 66.66%; 66.66% and 56.66% each in group A, B and C respectively (p >0.05). Mean age in group A was 7.3±7.16; in group B 5.92±5.40 and in group C it was 7.43±5.95. Majority of children were male in all the groups i.e. 80%; 66.66% and 76.66% respectively (p>0.05).

Table I shows various findings observed among the study cases at the time of admission. With regard to general status of children, it was found to be comparable in maximum number of children (p>0.05). Sensorium was not altered in 93.33%, 90% and 96.67% of three groups respectively with no significant difference (p>0.05). No convulsions were reported in any of the groups. Mean respiratory rate noted was 57.03±9.17; 58.63±5.63 and 58.23±8.94 in three groups respectively. Retractions were found in 19, 14 and 11 patients respectively. Nasal flaring was mild and rarely found in 13, 19 and 14 patients. Oxygen saturation was 89.06±3.32; 87.96±3.47 and 88.1±3.99 in three groups respectively. Cough was present in 100% of the cases of all the three groups. Crepts were found in 90%; 86.66% and 83.33% patients, use of accessory muscles was noted in 24, 26 and 23 patients each in three groups. All the findings at the time of admission were found to be comparable and found insignificant (p.0.05).

Table II shows various findings observed after 24 hours of admission. General status of children was found to be normal in 9 patients in group C as compared to group A and B and it was statistically significant. Similarly, sensorium was normal in less number of patients in group C with insignificant difference (p>0.05). No convulsions were noted in any of the patients after 24 hours. Cough was present in all the patients; crepts in 90%, 60% and 79.71% patients of three groups respectively.

Table III shows total number of patients who discontinued from the study after 24 hours due to various reasons. In the present study, 3 patients in group A discontinued due to tachycardia while none of the patients discontinued due to tachycardia in hypertonic and normal saline group showing significant difference. Two patients in group A, 3 in group B and 4 in group C were declared as treatment failure due to worsened score. On statistical comparison, no significant difference was observed (p>0.05). Mean duration of hospital stay in hours in

group A was 57.1±18.94; in group B 55.70±9.92 and in group C 74.82±22.29. On statistical comparison; it was found that there was a significant difference between all the three groups.

Table IV shows total score at the time of admission in all the groups; after 24 hours and after discharge. We observed a 70.14% percent improvement from at the time of admission to after 24 hours and 159.25% change after discharge from the time of admission in group A. In group B, we found a 64.64% percent improvement from at the time of admission to after 24 hours and 157.64% improvement after discharge from the time of admission in group B. Similarly in group C; we found 16.30% percent improvement from at the time of admission to after 24 hours and 152.01% change after discharge. Thus, we observed a significant improvement in adrenaline group (group A) and 3% hypertonic saline group (group B) as compared to normal saline group (group C) patients and further it was found that adrenaline group (group A) cases had higher change as compared to 3% hypertonic saline (group B).

DISCUSSION

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants up to two years of age, leading to 1.9 million deaths in children per year in developing countries with 20% of these deaths occurring in India.[10] ALRTI (most commonly viral infections) is the leading cause of under-five mortality globally.[11] India loses nearly 1 lakh children due to ALRTI every year.[12]

RSV is the major cause of bronchiolitis in infancy. In a study involving 1148 children, the peak age of incidence was 2 to 6 months, with more than 80% of the cases occurring during the first year of life.[13] Bronchiolitis occurs more frequently in boys; the male to female ratio is approximately 1.5:1.[14] Prematurity, infants on top feeds, attending daycare centers, exposure to smoking at home, overcrowded living conditions, having preschool age siblings with upper respiratory tract infection, those with underlying heart or lung or immunological problems and children with Trisomy 21 with or without congenital heart disease are at increased risk. It is in the majority of cases, a mild and self-limiting illness that can be managed on ambulatory basis with supportive care (supplemental oxygen, IV fluids, saline) alone. Multiple intervention studies have been carried out to improve treatment of bronchiolitis. Various modalities like nebulized bronchodilators (epinephrine/salbutamol), Hypertonic saline, Dexamethasone + Inhaled epinephrine, Surfactant, Heliox , Aerosolized Ribavirin, Oral bronchodilators, Montelukast, Inhaled/Systemic corticosteroids, Chest physiotherapy, Antibiotics , Steam inhalation, RSV polyclonal immunoglobulin / Palivizumab have been studied over the past few years.

Currently there standard treatment remains supportive care. Nebulized adrenaline is currently used as the preferred treatment in addition to supportive care, but it causes tachycardia as the potential side effect. Nebulised hypertonic saline and normal saline may be a beneficial treatment to manage acute bronchiolitis because they can improve airway hygiene with an efficacy equivalent to nebulized adrenaline, but without tachycardia. But not much of studies have been done to compare the efficacy and side effects of these three simultaneously. This study is needed to assess the efficacy of hypertonic (3%) saline and normal saline solution administered via a nebuliser in infants with acute bronchiolitis, compared with adrenaline.

In the present study 90 children of either sex, aged 2 months to 2 years, presenting with an episode of acute bronchiolitis and respiratory distress to our hospital emergency room were enrolled on successive basis in either of three groups. Clinical scoring system described by Uyan *et al* was used.[9] Clinical score is generally considered a relatively objective measure to assess the severity of illness.

In the present study majority of children were upto 6 months of age in all the groups i.e. 66.66%; 66.66% and 56.66% each in group A, B and C respectively with no statistically significant difference , ($p > 0.05$). Mean age in group A was 7.3±7.16; in group B 5.92±5.40 and in group C it was 7.43±5.95. In a study involving 1148 children, the peak age of incidence was 2 to 6 months, with more than 80% of the cases occurring during the first year of life.[13]

Majority of children were male in all the groups i.e. 80%; 66.66% and 76.66% respectively with no statistically significant difference,($p>0.05$). Bronchiolitis occurs more frequently in boys; the male to female ratio is approximately 1.5:1.[14]

At the time of admission all the groups were having nearly similar mean heart rate 125.8±15.35, 133.26±14.75, 125.08±11.03; respiratory rate 57.03±9.17; 58.63±5.63, 58.23±8.94; Oxygen

saturation 89.06±3.32; 87.96±3.47 and 88.1±3.99 in three groups respectively with no statistically significant difference. Total score at the the time of admission was 7.76±2.40, 7.43±2.19, 7.63±2.47 in group A, B, C respectively.

After 24 hours of admission: general status of children was found to be normal in less number of patients in group C (9 patients) as compared to group A (21 patients) and B (23 patients) and it was statistically significant ($p<0.01$). Total score after 24 hours decreased to 3.73±3.23, 3.8±2.86 and 6.48±2.18 in group A, B, C respectively. We observed a 70.14% percent improvement after 24 hours. In group B, we found a 64.64% percent improvement after 24 hours. Similarly in group C; 16.30% percent improvement was found after 24 hours. Thus, we observed a significant improvement in adrenaline group (group A) and hypertonic saline group (group B) as compared to normal saline group (group C) patients. Hence we concluded that hypertonic saline and adrenaline are equally effective in treating bronchiolitis but more effective than normal saline.

In a double blind RCT, Mandelberg and colleagues concluded that in infants hospitalized with viral bronchiolitis, aerosolized 3% saline solution plus 1.5 mg Epinephrine decreases symptoms and length of hospitalization as compared to 0.9% saline solution plus 1.5 mg Epinephrine.[15]

The Cochrane Review on hypertonic saline showed it not only reduces the duration of hospitalization but also improves clinical symptom scores in acute bronchiolitis. 3% hypertonic saline is a relatively inexpensive treatment but the potential economic and social gain is enormous,[16]

In another double blind RCT, Sarrell and colleagues determined that in nonasthmatic, non-severely ill ambulatory infants with viral bronchiolitis, aerosolized 3% saline solution plus 5 mg terbutaline is effective in decreasing symptoms as compared to 0.9% saline solution plus 5 mg terbutalin.[17]

Kuzik and colleagues concluded that the use of nebulized 3% HS in addition to routine therapy is a safe, inexpensive, and effective treatment for infants hospitalized with moderately severe viral bronchiolitis.[16]

Another meta-analysis of 19 trials (2256 participants) compared nebulized epinephrine with placebo or other bronchodilators. Epinephrine versus placebo among outpatients showed a significant reduction in admissions at Day 1 but not at Day 7 post-emergency department visit. This review demonstrated the superiority of epinephrine compared to placebo for short-term outcomes for outpatients, particularly in the first 24 hours of care, but there was no evidence to support the use of epinephrine for inpatients.[18]

But a randomized, double-blind, controlled trial by Wainwright *et al* [5] and Skejerven *et al* [19] compared nebulizer single-isomer epinephrine with placebo contradicted and showed that the use of nebulized epinephrine did not significantly reduce the length of the hospital stay or the time until the infant was ready for discharge among infants admitted to the hospital with bronchiolitis.

Hypertonic saline might have reversed some pathophysiological abnormalities by decreasing epithelial edema, improving elasticity and viscosity of mucus and thus improving airway clearance. Mucociliary clearance is presumed to be decreased in bronchiolitis. Recently, it has been proposed that dehydration of the airway surface liquid is part of the pathophysiology of viral bronchiolitis. In a systematic review by Wark and McDonald[20] in 143 subjects in seven trials in subjects with cystic fibrosis supported role of nebulised hypertonic saline in improving mucociliary clearance immediately after Airway edema and mucus plugging are the predominant pathological features in infants with acute viral bronchiolitis. Hypertonic saline induces an osmotic flow of water into mucus layer, rehydrates secretions and improves mucus rheology; lowers the viscosity by breaking the ionic bonds within the mucus; stimulates cilia beat via the release of prostaglandin E2.

Grewal *et al* (2009) and Susan *et al* (2014) contradicted by concluding that hypertonic[21] saline and epinephrine did not improve clinical outcome any more than normal saline and epinephrine in the emergency setting.[22] Florin *et al* in 2014 did a double blind RCT including 31 children concluded that the infants with bronchiolitis and persistent respiratory distress after standard treatment in the emergency department had less improvement after receiving 3% HS compared with those who received NS.[23] Mark *et al* (2014) did a multi-centre parallel-group, pragmatic RCT in ten UK hospitals. concluded that this study does not support the use of nebulised HS in the treatment of acute bronchiolitis over usual care with minimal handlings.[24] AAP recommendations

2014 also recommends Nebulized hypertonic saline should not be administered to infants with a diagnosis of bronchiolitis in the emergency department but clinicians may administer nebulized hypertonic saline to infants and children hospitalized for bronchiolitis.[25] Malik G *et al* compared the effects of nebulised 3% hypertonic saline, 0.9% saline and salbutamol in patients of acute bronchiolitis and concluded that 3% Hypertonic Saline nebulization is an effective and safe treatment in patients of acute bronchiolitis.[26] Another systematic review by Zhang and colleagues concluded that nebulized hypertonic saline is a safe and potentially effective treatment of infants with acute bronchiolitis.[27]

Two patients were excluded from the study due to worsened score in group A, 3 in group B and 4 in group C. On statistical comparison, no significant difference observed ($p>0.05$). Three patients in group A were excluded due to tachycardia while none of them was excluded in group B or C and showing significant difference among three groups , concluding that adrenaline had a disadvantage of tachycardia over 3% hypertonic saline and normal saline.

Mean duration in hours in group A was 57.1±18.94; in group B 55.70±9.92 and in group C 74.82±22.29. On statistical comparison; group A vs. B, we found no significant difference among two groups but when we compared group B vs. group C, it was found to be highly significant ($p<0.001$). Further, we compared group A vs. group C, it was also found to be significant ($p <0.01$) concluding that nebulisation with adrenaline and 3% hypertonic saline was superior to normal saline. Patients treated only with nebulised normal saline had a statistically significant longer duration of stay as compared to the other 2 groups. Adrenaline and hypertonic saline reduced the duration of stay by 17 and 19 hours respectively.

Guy *et al* (2006) and a cochrane based systematic review (2011) including 4 RCTs involving 581 infants compared 3% saline with 0.9% saline and concluded that nebulization with 3% saline results in a significantly shorter length of hospital stay as well as a lower clinical score.[21]

A systematic review published in Indian Pediatrics and study by Luo *et al* looking at hypertonic saline against placebo found significant reduction in duration of hospital stay in the hypertonic saline group. Duration of hospitalization was shorter by 0.94 days with hypertonic saline group although there was no difference in admission rates when sued in out-patients.[28]

Use of 3% hypertonic saline was safe in our study and was not associated with any other adverse event. Ansari *et al* compared the efficacy and safety of 5%, 3%, and 0.9% saline solution for treating acute bronchiolitis and concluded that Nebulization with 5% hypertonic saline is safe, can be widely generalizable, and may be superior to current treatment for early outpatient treatment of bronchiolitis.[29] Anil *et al* investigated the effectiveness of nebulized salbutamol, epinephrine, 3% saline, and normal saline (0.9% NaCl) inferred that improved clearance of mucus in airway may be function of total mass of normal saline rather than concentration of normal saline.[30]

CONCLUSION

Among hospitalized infants with non-severe acute bronchiolitis nebulized 3% saline significantly reduces clinical severity score among inpatients with mild to moderate bronchiolitis. Given the clinically relevant benefit and good safety profile, nebulized 3% saline used should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis. Further large randomized controlled trials, preferably multi-centered, are still required to evaluate the effectiveness of nebulizer hypertonic saline in infants with acute viral bronchiolitis, principally in infants who attend the emergency department and infants hospitalized with severe acute bronchiolitis. The optimal delivery intervals, duration of treatment and concentration of saline, and the most effective delivery devices remain to be determined. The mechanism of action of nebulized hypertonic saline in patients with viral bronchiolitis also needed to be addressed in future studies. Given the high prevalence of viral bronchiolitis in infants and the tremendous burden of this illness related to hospitalization use of 3% hypertonic saline may potentially have a positive economic impact for both the health system and the individual families.

Table I
Various findings noted amongst three study groups on admission (n=30)

Parameters	Group A (Nebulised Epinephrine) n(%)	Group B (Nebulised (3%) hypertonic saline) n(%)	Group C (Normal saline) n(%)	Statistical significance
General status				
Normal	2(6.66%)	3(10%)	0	$\chi2 = 6.93$; p=0.327
Mod. uneasy/occ. Crying	19(63.33%)	21(70%)	21(70%)	NS
Very uneasy/crying cont.	8(%)	4(13.33%)	9(30%)	
Lethargic	1(3.33%)	2(6.66%)	0	
Sensorium				$\chi2 = 1.07$; p=0.585
Normal	28(93.33%)	27(90%)	29(96.66%)	NS
Altered	2(6.66%)	3(10%)	1(3.33%)	
Convulsions				
Yes	0	0	0	-
No	30(100%)	30(100%)	30(100%)	
Respiratory rate				
< 30	0	0	0	
30-45	4(13.33%)	0	4(13.33%)	$\chi2 = 4.93$; p=0.294
45-60	15(50%)	19(63.33%)	14(46.66%)	NS
>60	11(36.66%)	11(36.66%)	12(40%)	
Mean respiratory rate	57.03±9.17	58.63±5.63	58.23±8.94	
Retractions				
No	1(3.33%)	0	0	$\chi2 = 8.59$; p=0.197
Only intercostals	10(33.33%)	16(53.33%)	18(60%)	NS
Intercostal, subcost., supraven.	19(63.33%)	14(46.66%)	11(36.66%)	
Abd. resp. Accomp.	0	0	1(3.33%)	
Wheezing				
No	17(56.66%)	19(63.33%)	14(46.66%)	$\chi2 = 3.40$; p=0.492
Heard only with stetho	12(40%)	8(26.66%)	14(46.66%)	NS
Resp. and Stetho	1(3.33%)	3(10%)	2(6.66%)	
Resp. without stetho.	0	0	0	
Nasal flaring				
No	6(20%)	4(13.33%)	8(26.66%)	$\chi2 = 4.22$; p=0.646
Mild and rarely	13(43.33%)	19(63.33%)	14(46.66%)	NS
Mod. To sev.	9(30%)	5(16.66%)	7(23.33%)	
Sev. And continuously	2(6.66%)	2(6.66%)	1(3.33%)	
Oxygen saturation	89.06±3.32	87.96±3.47	88.1±3.99	
Rhinitis				$\chi2 = 3.33$; p=0.188
Yes	22(73.33%)	27(90%)	22(73.33%)	NS
No	8(26.66%)	3(10%)	8(26.66%)	
Cough				
Yes	30(100%)	30(100%)	30(100%)	-
No	0	0	0	
Crepts				$\chi2 = 0.576$; p=0.749
Yes	27(90%)	26(86.66%)	25(83.33%)	NS
No	3(10%)	4(13.33%)	5(16.66%)	
Use of accessory muscles				$\chi2 = 1.01$; p=0.601
Yes	24(80%)	26(86.66%)	23(76.66%)	NS
No	6(20%)	4(13.33%)	7(23.33%)	
Heart rate	125.8±15.35	133.26±14.75	125.08±11.03	0.04 S
SBP	81.13±7.78	78.33±8.85	79.2±6.22	0.357; NS
DBP	58±5.94	59.4±5.12	57.46±5.89	0.395; NS
Total score	7.76±2.40	7.43±2.19	7.63±2.47	0.862; NS

Table II
Various findings noted amongst three study groups after 24 hours (n=30)

Parameters	Group A (Nebulised Epinephrine) n(%)	Group B (Nebulised (3%)hypertonic saline) n(%)	Group C* (Normal saline) (n=29) n(%)	Statistical significance
General status				
Normal	21(70%)	23(76.66%)	9(30%)	$\chi2 = 16.39$; p
Mod. uneasy/occ. Crying	6(20%)	5(16.66%)	17(56.66%)	<0.01 S
Very uneasy/crying cont.	3(10%)	2(6.66%)	3(10%)	
Lethargic	0	0	0	
Sensorium				$\chi2 = 0.578$;
Normal	29(96.66%)	29(96.66%)	27(93.10%)	p=0.748
Altered	1(3.33%)	1(3.33%)	2(6.89%)	NS
Convulsions				
Yes	0	0	0	-
No	30(100%)	30(100%)	29(100%)	
Respiratory rate				
< 30	2(6.66%)	0	0	$\chi2 = 13.20$; p
30-45	15(50%)	16(53.33%)	6(20.68%)	<0.05 S
45-60	10(33.33%)	10(33.33%)	15(51.72%)	
>60	3(10%)	4(13.33%)	8(27.58%)	
Mean respiratory rate	45.5±9.86	48.86±8.23	53.41±8.78	
Retractions				
No	15(50%)	10(33.33%)	0	$\chi2 = 22.31$; p
Only intercostals	11(36.66%)	17(56.66%)	22(75.86%)	<0.001 HS
Intercostal, subcost., supraven.	3(10%)	2(6.66%)	7(24.13%)	
Abd. resp. Accomp.	1(3.33%)	1(3.33%)	0	
Wheezing				
No	10(33.33%)	14(46.66%)	0	$\chi2 = 22.33$; p
Heard only with stetho	15(50%)	13(43.33%)	18(62.06%)	<0.001 HS
Resp. and Stetho	4(13.33%)	3(10%)	11(37.93%)	
Resp. without stetho.	1(3.33%)	0	0	
Nasal flaring				
No	19(63.33%)	18(60%)	7(24.13%)	$\chi2 = 21.03$; p
Mild and rarely	8(26.66%)	9(30%)	18(62.06%)	<0.001 HS
Mod. To sev.	3(10%)	0	4(13.79%)	
Sev. And continuously	0	3(10%)	0	
Oxygen saturation	93.7±3.37	88.96±3.46	91.79±4.02	
Rhinitis				$\chi2 = 0.825$;
Yes	20(66.66%)	18(60%)	16(55.17%)	p=0.662
No	10(33.33%)	12(40%)	13(44.82%)	NS
Cough				
Yes	30(100%)	30(100%)	29(100%)	-
No	0	0	0	
Crepts				$\chi2 = 7.68$; p
Yes	27(90%)	18(60%)	23(79.71%)	<0.05 S
No	3(10%)	12(40%)	6(20.68%)	
Use of accessory muscles				
Yes	10(33.33%)	11(36.66%)	15(51.72%)	$\chi2 = 2.33$;
No	20(66.66%)	19(63.33%)	14(48.27%)	p=0.310 NS
Heart rate	137.46±24.14	116.86±16.01	117.20±13.31	<0.001 HS
SBP	83.13±6.48	78.6±9.70	78.96±7.37	<0.05 S
DBP	60.6±4.87	58.2±7.11	59.72±6.40	>0.05 NS
Total score	3.73±3.23	3.8±2.86	6.48±2.18	

* One patient refused to participate after 16 hours of admission

Table III
Total number of treatment failures from the study after 24 hours

Criteria	Group A (Nebulised Epinephrine) n(%)	Group B (Nebulised (3%)hypertonic saline) n(%)	Group C (Normal saline) n(%)	Statistical significance
Tachycardia	3(10%)	0	0	$\chi 2=0.7.51$; p=0.111 NS
Worsened score	2(6.66%)	3(10%)	4(13.33%)	
Total	5(16.66%)	3(10%)	5(16.66%)	

Table IV
Final score of patients amongst three study groups (n=30)

Age range (months)	Group A (Nebulised Epinephrine) n(%)	% change	Group B (Nebulised 3% hypertonic saline) n(%)	% change	Group C (Normal saline) n(%)	% change
Total score At the time of admission	7.76±2.40		7.43±2.19		7.63±2.47	
Total score after 24 hours	3.73±3.23	70.14	3.8±2.86	64.64	6.48±2.18	16.30
Total score after discharge	0.88±0.52	159.25	0.88±0.69	157.64	1.04±0.73	152.01

DISCUSSION

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants up to two years of age, leading to 1.9 million deaths in children per year in developing countries with 20% of these deaths occurring in India.[10] ALRTI (most commonly viral infections) is the leading cause of under-five mortality globally.[11] India loses nearly 1 lakh children due to ALRTI every year.[12]

RSV is the major cause of bronchiolitis in infancy. In a study involving 1148 children, the peak age of incidence was 2 to 6 months, with more than 80% of the cases occurring during the first year of life.[13] Bronchiolitis occurs more frequently in boys; the male to female ratio is approximately 1.5:1.[14] Prematurity, infants on top feeds, attending daycare centers, exposure to smoking at home, overcrowded living conditions, having preschool age siblings with upper respiratory tract infection, those with underlying heart or lung or immunological problems and children with Trisomy 21 with or without congenital heart disease are at increased risk. It is in the majority of cases, a mild and self-limiting illness that can be managed on ambulatory basis with supportive care (supplemental oxygen, IV fluids, saline) alone. Multiple intervention studies have been carried out to improve treatment of bronchiolitis. Various modalities like nebulized bronchodilators (epinephrine/salbutamol), Hypertonic saline, Dexamethasone + Inhaled epinephrine, Surfactant, Heliox , Aerosolized Ribavirin, Oral bronchodilators, Montelukast, Inhaled/Systemic corticosteroids, Chest physiotherapy, Antibiotics , Steam inhalation, RSV polyclonal immunoglobulin / Palivizumab have been studied over the past few years.

Currently there standard treatment remains supportive care. Nebulized adrenaline is currently used as the preferred treatment in addition to supportive care, but it causes tachycardia as the potential side effect. Nebulised hypertonic saline and normal saline may be a beneficial treatment to manage acute bronchiolitis because they can improve airway hygiene with an efficacy equivalent to nebulized adrenaline, but without tachycardia. But not much of studies have been done to compare the efficacy and side effects of these three simultaneously. This study is needed to assess the efficacy of hypertonic (3%) saline and normal saline solution administered via a nebuliser in infants with acute bronchiolitis, compared with adrenaline.

In the present study 90 children of either sex, aged 2 months to 2 years, presenting with an episode of acute bronchiolitis and respiratory distress to our hospital emergency room were enrolled on successive basis in either of three groups. Clinical scoring system described by Uyan *et al* was used.[9]

Clinical score is generally considered a relatively objective measure to assess the severity of illness.

In the present study majority of children were upto 6 months of age in all the groups i.e. 66.66%; 66.66% and 56.66% each in group A, B and C respectively with no statistically significant difference , ($p > 0.05$). Mean age in group A was 7.3±7.16; in group B 5.92±5.40 and in group C it was 7.43±5.95. In a study involving 1148 children, the peak age of incidence was 2 to 6 months, with more than 80% of the cases occurring during the first year of life.[13]

Majority of children were male in all the groups i.e. 80%; 66.66% and 76.66% respectively with no statistically significant difference,($p>0.05$). Bronchiolitis occurs more frequently in boys; the male to female ratio is approximately 1.5:1.[14]

At the time of admission all the groups were having nearly similar mean heart rate 125.8±15.35, 133.26±14.75, 125.08±11.03; respiratory rate 57.03±9.17; 58.63±5.63, 58.23±8.94; Oxygen saturation 89.06±3.32; 87.96±3.47 and 88.1±3.99 in three groups respectively with no statistically significant difference. Total score at the the time of admission was 7.76±2.40, 7.43±2.19, 7.63±2.47 in group A, B, C respectively.

After 24 hours of admission: general status of children was found to be normal in less number of patients in group C (9 patients) as compared to group A(21 patients) and B(23 patients) and it was statistically significant ($p<0.01$). Total score after 24 hours decreased to 3.73±3.23, 3.8±2.86 and 6.48±2.18 in group A,B,C respectively. We observed a 70.14% percent improvement after 24 hours. In group B, we found a 64.64% percent improvement after 24 hours. Similarly in group C; 16.30% percent improvement was found after 24 hours. Thus, we observed a significant improvement in adrenaline group (group A) and hypertonic saline group (group B) as compared to normal saline group (group C) patients. Hence we concluded that hypertonic saline and adrenaline are equally effective in treating bronchiolitis but more effective than normal saline.

In a double blind RCT, Mandelberg and colleagues concluded that in infants hospitalized with viral bronchiolitis, aerosolized 3% saline solution plus 1.5 mg Epinephrine decreases symptoms and length of hospitalization as compared to 0.9% saline solution plus 1.5 mg Epinephrine.[15]

The Cochrane Review on hypertonic saline showed it not only reduces the duration of hospitalization but also improves clinical symptom scores in acute bronchiolitis. 3% hypertonic saline is a relatively inexpensive treatment but the potential economic and social gain is enormous,[16]

In another double blind RCT, Sarrell and colleagues determined that in nonasthmatic, non-severely ill ambulatory infants with viral bronchiolitis, aerosolized 3% saline solution plus 5 mg terbutaline is effective in decreasing symptoms as compared to 0.9% saline solution plus 5 mg terbutalin.[17]

Kuzik and colleagues concluded that the use of nebulized 3% HS in addition to routine therapy is a safe, inexpensive, and effective treatment for infants hospitalized with moderately severe viral bronchiolitis.[16]

Another meta-analysis of 19 trials (2256 participants) compared nebulized epinephrine with placebo or other bronchodilators. Epinephrine versus placebo among outpatients showed a significant reduction in admissions at Day 1 but not at Day 7 post-emergency department visit. This review demonstrated the superiority of epinephrine compared to placebo for short-term outcomes for outpatients, particularly in the first 24 hours of care, but there was no evidence to support the use of epinephrine for inpatients. [18]

But a randomized, double-blind, controlled trial by Wainwright *et al* [5] and Skejerven *et al* [19] compared nebulizer single-isomer epinephrine with placebo contradicted and showed that the use of nebulized epinephrine did not significantly reduce the length of the hospital stay or the time until the infant was ready for discharge among infants admitted to the hospital with bronchiolitis.

Hypertonic saline might have reversed some pathophysiological abnormalities by decreasing epithelial edema, improving elasticity and viscosity of mucus and thus improving airway clearance. Mucociliary clearance is presumed to be decreased in bronchiolitis. Recently, it has been proposed that dehydration of the airway surface liquid is part of the pathophysiology of viral bronchiolitis. In a systematic review by Wark and McDonald[20] in 143 subjects in seven trials in subjects with cystic fibrosis supported role of nebulised hypertonic saline in improving mucociliary clearance immediately after Airway edema and mucus plugging are the predominant pathological features in infants with

acute viral bronchiolitis. Hypertonic saline induces an osmotic flow of water into mucus layer, rehydrates secretions and improves mucus rheology; lowers the viscosity by breaking the ionic bonds within the mucus; stimulates cilia beat via the release of prostaglandin E2.

Grewal *et al* (2009) and Susan *et al* (2014) contradicted by concluding that hypertonic[21] saline and epinephrine did not improve clinical outcome any more than normal saline and epinephrine in the emergency setting.[22] Florin *et al* in 2014 did a double blind RCT including 31 children concluded that the infants with bronchiolitis and persistent respiratory distress after standard treatment in the emergency department had less improvement after receiving 3% HS compared with those who received NS.[23] Mark *et al* (2014) did a multi-centre parallel-group, pragmatic RCT in ten UK hospitals. concluded that this study does not support the use of nebulised HS in the treatment of acute bronchiolitis over usual care with minimal handlings.[24] AAP recommendations 2014 also recommends Nebulized hypertonic saline should not be administered to infants with a diagnosis of bronchiolitis in the emergency department but clinicians may administer nebulized hypertonic saline to infants and children hospitalized for bronchiolitis.[25] Malik G *et al* compared the effects of nebulised 3% hypertonic saline, 0.9% saline and salbutamol in patients of acute bronchiolitis and **concluded that** 3% Hypertonic Saline nebulization is an effective and safe treatment in patients of acute bronchiolitis.[26] Another systematic review by Zhang and colleagues **concluded that** nebulized hypertonic saline is a safe and potentially effective treatment of infants with acute bronchiolitis.[27]

Two patients were excluded from the study due to worsened score in group A, 3 in group B and 4 in group C. On statistical comparison, no significant difference observed ($p>0.05$). Three patients in group A were excluded due to tachycardia while none of them was excluded in group B or C and showing significant difference among three groups , concluding that adrenaline had a disadvantage of tachycardia over 3% hypertonic saline and normal saline.

Mean duration in hours in group A was 57.1±18.94; in group B 55.70±9.92 and in group C 74.82±22.29. On statistical comparison; group A vs. B, we found no significant difference among two groups but when we compared group B vs. group C, it was found to be highly significant ($p<0.001$). Further, we compared group A vs. group C, it was also found to be significant ($p <0.01$) concluding that nebulisation with adrenaline and 3% hypertonic saline was superior than normal saline. Patients treated only with nebulised normal saline had a statistically significant longer duration of stay as compared to the other 2 groups. Adrenaline and hypertonic saline reduced the duration of stay by 17 and 19 hours respectively.

Guy *et al* (2006) and a cochrane based systematic review (2011) including 4 RCTs involving 581 infants compared 3% saline with 0.9% saline and concluded that nebulization with 3% saline results in a significantly shorter length of hospital stay as well as a lower clinical score.[21]

A systematic review published in Indian Pediatrics and study by Luo *et al* looking at hypertonic saline against placebo found significant reduction in duration of hospital stay in the hypertonic saline group. Duration of hospitalization was shorter by 0.94 days with hypertonic saline group although there was no difference in admission rates when sued in out-patients.[28]

Use of 3% hypertonic saline was safe in our study and was not associated with any other adverse event. Ansari *et al* compared the efficacy and safety of 5%, 3%, and 0.9% saline solution for treating acute bronchiolitis and concluded that Nebulization with 5% hypertonic saline is safe, can be widely generalizable, and may be superior to current treatment for early outpatient treatment of bronchiolitis.[29] Anil *et al* investigated the effectiveness of nebulized salbutamol, epinephrine, 3% saline, and normal saline (0.9% NaCl) inferred that improved clearance of mucus in airway may be function of total mass of normal saline rather than concentration of normal saline.[30]

CONCLUSION

Among hospitalized infants with non-severe acute bronchiolitis nebulized 3% saline significantly reduces clinical severity score among inpatients with mild to moderate bronchiolitis. Given the clinically relevant benefit and good safety profile, nebulized 3% saline used should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis. Further large randomized controlled trials, preferably multi-centered, are still

required to evaluate the effectiveness of nebulizer hypertonic saline in infants with acute viral bronchiolitis, principally in infants who attend the emergency department and infants hospitalized with severe acute bronchiolitis. The optimal delivery intervals, duration of treatment and concentration of saline, and the most effective delivery devices remain to be determined. The mechanism of action of nebulized hypertonic saline in patients with viral bronchiolitis also needed to be addressed in future studies. Given the high prevalence of viral bronchiolitis in infants and the tremendous burden of this illness related to hospitalization use of 3% hypertonic saline may potentially have a positive economic impact for both the health system and the individual families.

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