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RCT Comparing 3% Hypertonic Saline & Normal Saline, When Given With L-Epinephrine Nebulisation in Management of Infants with Moderate to Severe Bronchiolitis.

Dr. Samiksha Sharma[1], Dr. Girijanand Jha[2], Dr. Binod Kr Singh[3], Dr Saroj Kumar,[4] Dr Sujit Kumar[5]

[1]*Senior Resident, Deptt of Pediatrics, N.M.C.H, Patna*
[2]*Senior Resident, Deptt of Pediatrics, N.M.C.H, Patna*
[3]*Professor & H.O.D, Deptt of Pediatrics, N.M.C.H, Patna*
[4]*Assistant Professor, Deptt of Pediatrics, N.M.C.H, Patna*
[5]*Associate Professor, Deptt of Pediatrics, N.M.C.H, Patna*
Corresponding author: Dr Girijanand Jha (girijanandjha@gmail.com)

Abstract:
Objective: *To compare 3% hypertonic saline and normal saline when given with L-epinephrine nebulisation in the management of infants with moderate to severe Bronchiolitis.*
Study design and setting: *Randomized controlled trial at a tertiary care teaching hospital (NMCH, Patna) over a period of 1.5 years.* ***Participants:*** *Hospitalized infants aged 6-12 months with bronchiolitis of moderate to severe severity.* ***Intervention:*** *Nebulization of 2 ml of 3% hypertonic saline alongwith 2 ml L-epinephrine (HS Group) or 2 mL of 0.9% saline along with 2 ml L-epinephrine (NS Group)* ***Results:*** *The two groups didn't differ significantly in their baseline characteristics. Mean clinical severity score at admission was 5.97 (SD=1.52) in HS group and 6.1 (SD=1.68) in NS group. Clinical severity scores monitored afterwards till discharge showed statistically significant improvement in 3% HS group at 24 hours (4.15 vs 4.88, p=0.04). However, afterwards the improvement was comparable in both the groups. Mean length of hospital stay (in hours) was 92.6 (range 52–244, SD 48.7) in HS group and 97.4 (range 56–264, S.D 51.3) in NS group (P=0.63). No significant change in serum sodium level or other serious adverse events were reported in either group.* ***Conclusion:*** *Both 3% HS and NS were effective and safe when used with L-epinephrine in the management of infants with moderate to severe bronchiolitis. Though HS induced better clinical improvement in the early hours of treatment, this improvement didn't translate into early discharge or decrease in length of hospital stay.*

Keywords: *clinical severity score, 3% saline, epinephrine, normal saline, nebulization, length of stay.*

Abbreviations: *AAP: American Academy of Pediatrics; CSS: clinical severity score; LOS: Length of stay; NS: Normal saline; SpO_2: Oxygen saturation by pulse oximetry; HR:Heart rate; RR: Respiratory rate.*

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I. Introduction:

Bronchiolitis is clinically defined as per the AAP consensus guidelines[1] as the first episode of acute wheezing in children less than two years of age, starting as a viral upper respiratory infection (coryza, cough or fever). This condition commonly leads to hospitalization in infancy and contributes to huge economic burden[2]. The standard treatment remains supportive care and includes ensuring adequate oxygen exchange, fluid intake and feeding of the infant[3]. Meta analyses of data on the most-used therapies for acute bronchiolitis namely, nebulized β2-agonsits, epinephrine, magnesium, glucocorticoids, and chest physiotherapy have failed to prove any conclusive beneficial effect on relevant clinical outcomes.[4,5,6,7] As a result, there is no unanimously accepted evidence driven treatment. However, these are the only vastly studied therapy for bronchiolitis and so still widely used[8]. Recently, researchers have reported the use of hypertonic saline therapy in such infants with variable benefits.[9,10] Though this modality being inexpensive promises to reduce the economic burden associated with the disease, there is paucity of data on comparison of important outcomes viz readiness for discharge, increase in serum sodium levels & other adverse events, which are important reflectors of morbidity. Also, there are only few studies which have specifically focused on various aspects of such treatment in infant age group, the greatest sufferers of this disease. With this background, we tried to find out if 3 % hypertonic saline would actually benefit infants with Bronchiolitis in a developing country.

II. Aims and Objectives

Aim: To compare 3% hypertonic saline and normal saline when given alongwith L-epinephrine nebulisation in infants with moderate to severe Bronchiolitis.

Objectives: 1. To compare the length of hospital stay in both the groups
2. To compare the improvement in clinical severity scores
3. To determine the occurrence of adverse events in both the groups

III. Methodology

Study setting: Infants admitted with bronchiolitis in I.P.D of Deptt of Pediatrics N.M.C.H Patna
Study duration: 1.5 years, from October 2018 to March 2020.
Study design: Double blinded Randomised control trial.
Inclusion criteria: In the present study, we included Infants visiting our OPD or ER who met clinical criteria of bronchiolitis and belonged to 6– 12 months age group and with a clinical severity score (CSS) of ≥4 and <11 as per Wang et al criteria[11] (Table 1).

Table 1: Clinical severity score

Study parameter	1 point	2 points	3 points
Respiratory rate/ minute	31–45	46–60	>60
Auscultatory wheeze	at terminal expiration using a stethoscope	during entire expiration or audible on expiration without stethoscope	Inspiratory & expiratory wheezing audible without stethoscope
Retraction	intercostal	tracheosternal	severe retraction with nasal flaring
General condition	normal	fair	irritability, lethargy, poor appetite

(<5=Mild disease,5-8= moderate disease, 9-12=severe disease)

Exclusion criteria: Infants with one or more of the following were excluded from the study:

SpO_2 <80% in room air by pulse oxymetry at presentation, prior chronic co-morbidities (cardiac, respiratory or neurological), prior wheezing episode, recent bronchodilator use (in the preceding 4 hours), recent steroid use (in preceding 48 hours), presence of symptoms >7 days, consolidation or atelectasis on chest X-ray or respiratory distress requiring mechanical ventilation at presentation.

After initial stabilization and clinical severity assessment, infants fit for inclusion in the study were enrolled. Data were collected in standardized forms to document pertinent history and physical examination**.** Infants were randomized in two groups (A and B) using a computer program and allocation was concealed. CSS, respiratory rate, SpO_2 in room air and heart rate were recorded at the time of admission, 15 minutes after each nebulisation and then hourly to 4 hourly as per clinical condition. Serum sodium level was investigated at the time of admission and then daily till discharge. Supplemental oxygen was provided by face mask to maintain SpO_2 > 92 %. All participants were given nebulisation (through a Jet nebulizer using a face mask) on two occasions at 30 min intervals at the time of admission & then every 6 hours interval until discharge. Group A was given nebulisation of L-Epinephrine 2 mg, diluted to 4 ml with 2 ml of 3 % Hypertonic Saline (HS) solution, whereas Group B received inhalation of L-Epinephrine 2 mg, diluted to 4 ml with 2 ml of 0.9 % Normal Saline solution. The infants were monitored for hypotension, tachycardia, tremor, improvement in clinical status and cough during administration of each dose. They were discharged if they met all of the following criteria: CSS <4, SpO2 >92% in room air for >8 hours and no feeding difficulty. Adverse events were defined as heart rate > 200, tremors, serum sodium >150mEq/L and worsening clinical status.

Statistical analysis: Data was entered in Microsoft excel and analyzed by SPSS software for Windows, version 19.0(SPSS Inc., Chicago). Dichotomous events were analyzed by Chi-Square test. Continuous variables were compared by Student t-test. P value less than 0.05 was considered significant.

IV. Results:

After initial screening, a total of 138 patients were assessed for eligibility out of which 40 were excluded as per our predefined criteria. So, 98 infants were enrolled in our study who were randomized into two groups of 49 each: Group A (Epinephrine+ 3% HS) and Group B (Epinephrine+ NS).

The two groups didn't differ statistically in terms of mean age, sex, passive smoking in family, family history of atopy or asthma, baseline CSS, heart rate, respiratory rate and SpO_2(Table 2).

Table 2: General baseline characteristics of the two groups

Parameters	Group A(n=49)	Group B (n=49)	p value
Age in months: Mean (S.D)	9.6 (1.41)	9.4 (1.49)	0.49
Male Gender	26(53%)	22(45%)	0.43
Passive smoking	9 (18.4%)	11 (22.4%)	0.62
Family history of atopy or asthma	9(18.4%)	8 (16.3%)	0.78
CSS at admission: Mean (S.D)	5.97(1.52)	6.1(1.68)	0.69
Heart rate at admission: Mean(S.D)	145.3(13.9)	147.7(17.1)	0.44
Respiratory rate at admission: Mean (S.D)	52.7(5.9)	51.3(5.4)	0.22
SpO_2 at admission: Mean (SD)	88.3 (4.1)	89.6 (4.2)	0.12

There was no statistically significant difference in the length of hospital stay in the two groups. Also, there was no significant difference in the serum sodium levels between the two groups either before treatment or after treatment. There was gradual improvement in CSS with time in both the groups and the effect was more pronounced in Group A as compared to Group B at 24 hours of therapy. Patients in group A (HS group) had more improvement in the CS scores at the end of 24 h of therapy and this difference was statistically significant ($p<0.05$). There was no significant difference in the mean changes in HR, RR and SpO2 between the two groups at the start of treatment, at the end of 24 h of therapy and at the time of discharge. No significant adverse events occurred in either of the treatment groups. No children were withdrawn from the trial due to side effects or clinical deterioration (Table 3).

Table 3: Outcome assessment:

Parameters	Group A(n=49)	Group B ()n=49	P value
LOS (hours): Mean; range (SD)	92.6 ; 52–244 (48.7)	97.4 (56–264) (51.3)	0.63
Sodium mEq/L before treatment: Mean (SD)	136.8 (3.18)	137.2 (2.92)	0.52
Sodium mEq/L after treatment: Mean (SD)	139.5 (3.8)	138.6 (3.32)	0.21
CSS at admission: Mean (S.D)	5.97(1.52)	6.1(1.68)	0.69
CSS at 1 hour: Mean (SD)	5.3 (1.48)	5.7 (1.56)	0.19
CSS at 24 hours: Mean (SD)	4.15 (1.7)	4.88 (1.8)	0.04
CSS at discharge: Mean (SD)	2.16 (0.33)	2.3 (0.35)	0.65
Heart rate at admission: Mean (S.D)	145.3(13.9)	147.7(17.1)	0.44
Heart rate at 24 hours: Mean (SD)	149.7 (12.1)	151.2 (14.4)	0.57
Heart rate at discharge: Mean (SD)	130.7 (5.8)	132.4 (6.3)	0.16
Respiratory rate at admission: Mean (S.D)	52.7(5.9)	51.3(5.4)	0.22
Respiratory rate at 24 hours: Mean (SD)	46.9 (5.7)	49.3 (5.3)	0.33
Respiratory rate at discharge: Mean (SD)	36.7 (4.8)	37.3 (4.9)	0.54
SpO2 at admission: Mean (SD)	88.3 (4.1)	89.6 (4.2)	0.12
SpO2 at 24 hours: Mean (SD)	91.4 (3.8)	90.8 (3.9)	0.44
SpO2 at discharge: Mean (S.D)	94.4 (2.1)	95.1(1.9)	0.08

V. Discussion:

Ours is one of the few studies conducted in tertiary care hospital of a developing country where we not only tried to look at the role of hypertonic saline in improving the CS scores but also studied its impact on reducing the length of hospital stay and hence early discharge eligibility. Strict inclusion and exclusion criteria were used to minimize possible confounding effects of uncharacterized and evolving wheezing phenotypes.

In both the groups, CSS improved by more than 20% in 24 hours suggesting that both treatment groups were effective. However, this improvement was more pronounced in 3% HS group at 24 hours($p<5\%$). Surprisingly, this improvement didn't translate into early discharge or decrease in length of hospital stay. This suggests that though there is no decrease in LOS, 3% HS does lead to earlier improvement in clinical condition. Previously, Sarrell et al[12]. had shown that substituting hypertonic saline for normal saline solution (2 ml) in the inhalation mixture for delivering bronchodilator improved clinical scores, but they had included only non severely ill children in their study. However Tal G et al[13] over a two year study period found that in hospitalized children with more severe bronchiolitis, nebulized 3% HS solution with epinephrine was found to be more effective treatment. Our findings are only somewhat consistent with the study of Wu et al.[14] who through a double blinded RCT concluded that HS given to children in the ED decreases hospital admissions but did not produce any significant difference in Respiratory Distress Assessment Instrument score or length of stay as compared to NS. Although Luo Z et al.[15] reported significant improvement in moderate to severe bronchiolitis infants with 3% HS as compared to NS, in their study they hadn't administered L-epinephrine. So, it can't be concluded from their study if addition of 3% HS actually benefitted infants over and above that provided by L-epinephrine. In our study all infants recovered in both the groups, there was no treatment failure or significant adverse events following nebulisation, as previously reported by Ralston et al.[16]

VI. Conclusion

3% HS is effective and safe when used with L-epinephrine in place of routine NS for managing infants with moderate to severe bronchiolitis. The improvement seemed to be more pronounced at 24 hours ($p<5\%$), suggesting that it is more beneficial than NS in the early hours of treatment. Surprisingly, this improvement didn't translate into early discharge or decrease in length of hospital stay. This suggests that though there is no decrease in LOS, 3% HS does lead to earlier improvement in clinical condition. This would help in better allocation of resources in the setting of a developing country. More studies are needed in multicentric settings with a larger sample size, involving moderate to severely affected patients, and with a placebo control design in order to confirm and extend our results.

Lmitations:

- The additional benefits(if any) of supportive care alone in infants with bronchiolitis couldn't be studied since we didn't have a placebo arm.
- We didn't study the most severe form of acute bronchitis who required direct PICU admission and patients with milder forms of the disease.
- We are also unsure about the confounding effects of co-inections if any.
- No RSV testing was done and sample size was small in the present study.

8.Conflict of Interest: non**e**

9.Financial Disclosure: The authors declare that this study hasn't received any financial support.

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