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Nebulized Hypertonic Saline for Treating Bronchiolitis in Infants – A Randomised Clinical Trial Conducted In Tertiary Care Teaching Hospital

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Abstract
Background*: Acute bronchiolitis is a common lower respiratory tract infection in infants which results from inflammatory obstruction of the small airways, Respiratory Syncytial Virus (RSV) being the main etiological agent.*
Aim and Objectives*: To compare the effectiveness of 3% HTS nebulization with 0.9% NS nebulization , In hospitalized children with acute bronchiolitis based on time for resolution of signs and symptoms Thereby duration of hospital stay.*
Study design*: A quasi randomized study.*
Materials and Methods*: Children admitted at Niloufer Hospital in PICU with clinical diagnostic criteria of bronchiolitis were randomized into two groups "1" and "2". "Group 1" subjects were administered 3% HTS nebulization for six doses while "Group 2" children were subjected to 0.9% NS over and above the other medication as required. Clinical severity score (CSS) was done before and after therapeutic intervention and resolution of signs and symptoms in the two groups were compared.*
Duration of study*: Nov 2013 – Oct 2014.*
Results*: The Pre intervention CSS score in 3%HTS group and 0.9% NS group is 10.36 ± 0.62 ; 10.33 ± 0.64 (p = 0.81) respectively. The CSS on day three when compared to day one were lowered by 75% in 3%HTS group and 50% in 0.9%NS group. The duration of hospital stay for the children treated with 3% HTS nebulization was decreased by 25% of average in 0.9% NS group, which is significant.*
Conclusion*: Nebulized 3% HTS therapy in children suffering from acute bronchiolitis is safe and early resolution of signs and symptoms led to decrease in hospital stay.*
Key Words*: Bronchiolitis, 3% hypertonic saline (HTS), 0.9% Normal saline (NS), Clinical Severity Score (CSS), Nebulization.*

I. Introduction

In India Acute Respiratory Infections (ARI) constitute a major public health problem and is the most important contributory factor to the mortality and morbidity in under 5 accounting for 15 – 34% of all childhood deaths. Children under 5 years of age, suffer about 5 episodes of ARI per year, thus averaging 238 million attacks consequently. India accounted for 28% of the mortality and 30% of Disability Adjusted Life Years (DALYs) lost due to ARIs as stated in the WHO World Health Report, 1995, bridging the Gaps[1]. The WHO figure of 1 out of 3 deaths due to — or associated with — ARI may be close to the real range of the ARI-proportional mortality in children of developing countries[2].

Acute bronchiolitis is a common lower respiratory tract infection (LRTI) among infants in tropical regions, including India. It comprises a significant proportion of all acute respiratory infections requiring hospitalisation. It is predominantly a viral disease. Respiratory syncitial virus is responsible for > 50 % cases [3].The diagnosis of acute bronchiolitis is usually based on clinical grounds. It refers to first episode of wheezing in children less than two years of age, starting as a viral upper respiratory tract infection (coryza, cough or fever) [4]. Although bronchiolitis results in hospitalisation of up to 1% of healthy infants and 2- 3% of high risk infants annually, the optimal treatment for bronchiolitis remain unclear. Hypertonic saline solution has been shown to increase mucociliary clearance in normal patients, in asthma, bronchiectasis, cystic fibrosis and sinonasal diseases (Daviskas 1996; Kellett 2005; Shoseyov 1998; Wark 2007). Such benefits would also be expected in infants with acute bronchiolitis (Mandelberg 2003)[5]. Although they may appear extremely ill on admission to the hospital, most infants with bronchiolitis, given adequate supportive care, are clinically improved within 3 to 4 days[6].There is lack of robust evidence for almost all the interventions that are usually tried, including inhaled epinephrine, bronchodilators, steroids, anticholinergics, antibiotics, surfactant and chest physiotherapy. It is suggested that hypertonic saline may be useful in bronchiolitis by absorbing water from the sub mucosa, thereby decreasing edema and improving mucociliary function. This modality may provide a cheap and effective therapy for children with acute bronchiolitis[7].

Hence a study has been proposed to answer the question "Does hypertonic saline nebulization (intervention) result in better response (outcome) compared to nebulization with normal saline, in infants with bronchiolitis (population)?". Scheffer[8] and colleagues demonstrated in vitro that the addition of hypertonic 3% saline markedly reduced sputum viscosity. King[9] and co-workers demonstrated that hypertonic saline reduced the viscoelasticity of sputum, compared to 0.9% saline. Sood[10] and associates demonstrated that hypertonic saline inhalations increase mucociliary clearance in normal volunteers, specifically through a cough-independent mechanism. Ciesla et al[11] demonstrated a decreased inflammatory response of polymorphonuclear leukocytes after pretreatment with hypertonic saline. Arbabi et al[12] demonstrated that prostacyclin, an agent with the potential to inhibit formation of thromboxane and the adhesion of leukocytes to endothelial cells, is produced in response to hypertonic saline and lipopolysaccharide.

II. Aims And Objectives

To compare the effectiveness of 3% hypertonic saline nebulization with 0.9% saline nebulization , in hospitalized children with acute bronchiolitis.

III. Material And Methods

One hundred and five children in the age group 2 months to 24 months, admitted in Paediatric Intensive Care Unit (PICU), in a tertiary care teaching hospital, during the period November 2013 to October 2014, fulfilling the clinical diagnostic criteria of bronchiolitis (as described by Panitch[4]) were included in the study.

Inclusion Criteria: Children from 2 months to 2 years of age with: First attack of wheezing, h/o coryza, cough, and fever, rhonchi / crackles on auscultation of chest, Clinical Severity score (CSS) {Wang}[13] of ≥ 4.
Exclusion Criteria: Previous episode of wheezing, h/o foreign body aspiration, Chronic cardio pulmonary disease, immunodeficiency, critically ill on admission with other associated illnesses, use of nebulized hypertonic saline in previous 12 hrs, premature birth with gestation age <34 weeks, progressive respiratory failure.
Informed written consent was taken from either of the parent before enrollment to the study.

All the 105 children with bronchiolitis in the study group were quasi randomly assigned to one of the groups: group 1 received Nebulization with 3% hypertonic saline (2.5ml) ; group 2 received Nebulization with 0.9% Normal saline (2.5ml) . Children were examined at the study entry and every day. The CSS score was recorded after the patient's oxygen had been removed for a total of 5 minutes. The treatment was given every 2 hours for 3 doses followed by every 4 hours for 5 doses followed by every 6 hours until discharge (based on clinical assessment).

All inhaled forms of therapies were delivered to a settled child from standard oxygen driven nebulizer through a tight fitting face mask or head box, whichever was better tolerated by the child. No detectable difference in color, smell, or other physical properties existed between 0.9% saline solution and 3% saline solution.

The decisions to discharge children were made at morning rounds by the attending physician, based on clinical grounds alone. The attending physician was blinded to the combination of the therapeutic package (3% saline solution vs 0.9% saline solution).

Clinical Severity Score (as described by Wang[13]1992)

Score	**0**	**1**	**2**	**3**
Respiratory rate Breaths / min	<30	31-45	46-60	>60
Wheezing	None	Terminal Expiratory or only with stethoscope	Entire Expiration or audible on expiration without stethoscope	Inspiratory & Expiratory Without stethoscope
Retraction	None	Intercostal only	Tracheosternal	Severe with Nasal flaring
General Condition	Normal	-	-	Irritable, lethargic, Poor feeding

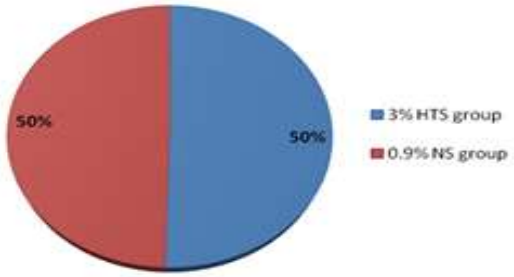
Outcome Measures:

Primary outcome was assessed by duration of hospital stay / Time for resolution of signs and symptoms and Clinical severity score.Secondary outcome was assessed by following parameters: Duration of O_2 supplementation,Requirement f add-on treatments ,Adverse Reactions e.g. Bronchospasm, hypertension, pallor, tremors, nausea, vomiting and urinary retention.

IV. Observations And Results

Total number of cases included in the study was 105 out of which 53 cases were treated with 3% hypertonic saline (HTS) and 52 cases were treated with 0.9%Normal saline (NS). 3 cases were subsequently deleted as they went on LAMA (1 case of NS group and 2 cases of HTS group).

CHART NO : 1 GROUP WISE DISTRIBUTION OF CASES



The commonest age group presented with bronchiolitis in the present study is 2-6 months (73.33%). The mean age group in months being 6.83 ± 4.69. Out of 105 cases 98 cases are seen below 1st year of life.

Table No: 1 Age & Sex Wise Distribution Of Children With Acute Bronchiolitis N=105.

Out of 105 cases studied 58 cases (55.23%) were male and 47 cases (44.76%) were female.

Age in months	Malen (%)	Femalen (%)	No of cases n (%)
2 – 6	44(41.90)	33(31.43)	77 (73.33)
>6 – 12	10(9.52)	11(10.47)	21(20.00)
>12 – 18	1(0.95)	3(2.85)	04 (3.80)
>18 – 24	3(2.85)	00	03 (2.85)
Total	58(55.23)	47(44.76)	105

Chart No: 2 Age & Sex Wise Distribution Of Cases

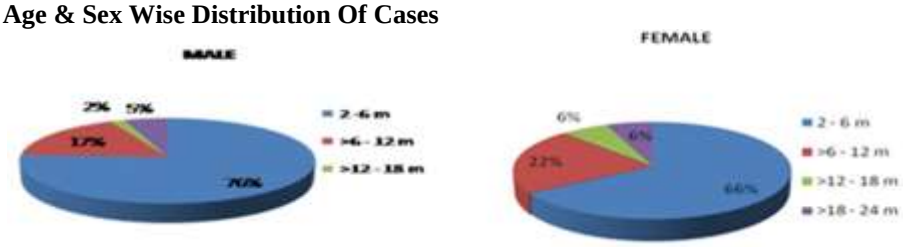


Table No – 2 Seasonal Distribution Of Cases With Bronchiolitis

Season	Frequency N(%)
July – October	24(22.85)
November – February	64(60.95)
March - June	17(16.20)

Out of 105 cases included in the study 61% presented between Nov – Feb (winter season).

Chart no: 4 seasonal distribution of cases with bronchiolitis

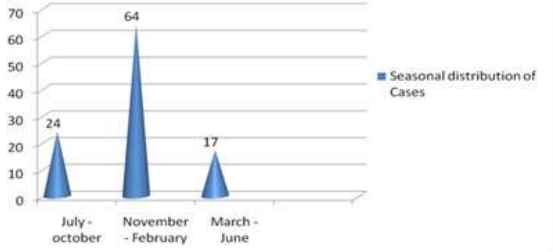


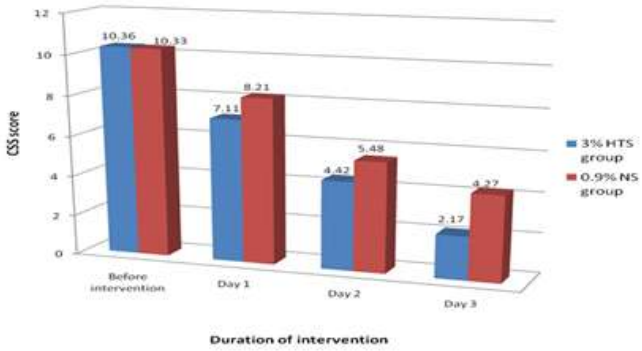
Table No: 3 Comparison Of Clinical Severity Score In Both The Groups Receiving Nebulization

Duration of intervention	Casestreatedwith3% HTS Mean ± SD n = 53	Cases treated with 0.9% NS Mean ± SD n = 52	Mean Difference (95% CI)
Pre Intervention	10.36 ± 0.62	10.33 ± 0.64	0.03(0.28 to -0.22)
DAY 1	7.11 ± 0.78	8.21 ± 0.75	-1.09(-0.83 to -1.39)*
DAY 2	4.42 ± 0.69	5.48 ± 0.85	-1.07 (-0.76 to 1.36)*
DAY 3	2.17 ± 0.38	4.27 ± 0.49	-2.09(-1.93 to -2.26)*

*p < 0.01

The Pre intervention CSS score in 3%HTS group and 0.9% NS group is 10.36 ± 0.62 ; 10.33 ± 0.64 (p = 0.81) respectively.On the first day of the treatment, after the intervention, the 3% HTS group had a lower CSS score compared to the 0.9% NS group, with a Mean difference of -1.09(-0.83 to -1.39) , p < 0.02).On the second day of treatment, the CSS scores in 3% HTS group and 0.9% NS group were 4.42 ± 0.69 & 5.48 ± 0.85 with a Mean difference of 1.07 (-0.76 to 1.36), p < 0.01).At the end of the day (Day 3) the CSS scores in 3% HTS group and 0.9 % NS group were 2.17 ± 0.38 & 4.27 ± 0.49 with a Mean difference of -2.09(-1.93 to – 2.26), p< 0.01).The clinical scores on day three when compared to day one were lowered by 75% in 3%HTS group and 50% in 0.9%NS group.

Chart No: 5 Comparison Of Clinical Severity Score In Both The Groups



No: 4 Outcome As Assessed By Duration Of Oxygen Supplementation

Outcome Parameters	Cases treated with 3% HTS nebulization Mean ± SDn = 53	Cases treated with 0.9% NS nebulization Mean ± SDn = 53	Mean Difference (95% CI)	P value
Duration of O2 supplementation in hours	24.38 ± 2.89	25.46 ± 3.32	-1.08(1.12 to -2.28)	0.077

The duration of oxygen supplementation in hours between both the intervention groups is almost equal and the difference is not significant as the p value between the groups is 0.077.

Table No: 5 No Of Cases Requiring Add On Treatments And Showing Adverse Reactions

Add on treatments	Cases treated with 3%HTS nebulisation n = 53	Cases treated with 0.9%NS nebulisation n = 52
Cases treated with epinephrine nebulisation	4	8
Cases treated with budecort nebulisation	2	6
Adverse reactions	Nil	Nil

Out of 53 cases in 3% HTS group, 4 cases required epinephrine nebulization and 2 cases required budecort nebulization. Out of 52 cases in NS group, 8 cases required epinephrine nebulization and 6 cases required budecort nebulization.

Table No: 6 Outcome As Assessed By Time For Resolution Of Signs And Symptoms

Outcome Parameters	Cases treated with 3% HTS nebulization Mean ± SDn = 53	Cases treated with 0.9% NS nebulization Mean ± SDn = 52	Mean Difference (95% CI)	P value
Time for resolution of signs and symptoms in hours	59.40 ± 6.24	75.77 ± 8.27	-16.37(-13.53 to -19.21)	0.02

The time for resolution of signs and symptoms for the children treated with 3% HTS nebulisation was decreased by 14.4% of average duration in cases treated with 3% HTS when compared to 0.9% NS group.

Chart No : 6 Time For Resolution Of Signs And Symptoms

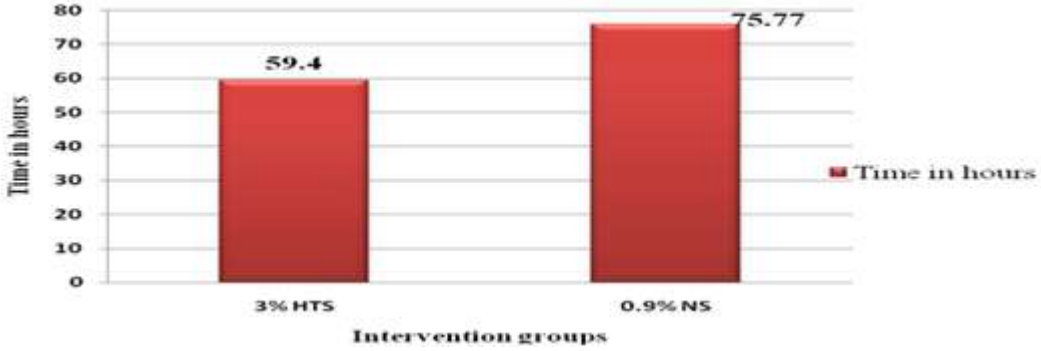
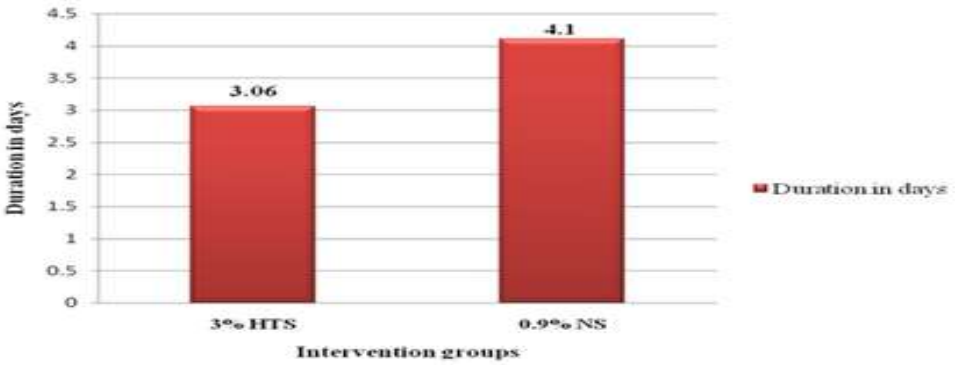


Table No: 7 Outcome As Assessed By Duration Of Hospital Stay

Outcome Parameters	Cases treated with 3% HTS nebulization Mean ± SDn = 53	Cases treated with 0.9% NS nebulization Mean ± SDn = 52	Mean difference (95% CI)	P value
Duration of hospital stay in days	3.06 ± 0.23	4.10 ± 0.36	-1.04(-0.92 to -1.15)	0.001

The duration of hospital stay for the children treated with 3% HTS nebulisation was decreased by 25% of average in 0.9% NS group, which is significant.

Chart No : 7 Duration Of Hospital Stay.



V. Discussion

All the 105 children were quasi randomly allocated interventions with either 3% HTS or 0.9% NS nebulization.

53 cases were treated with 3% HTS nebulization and 52 cases were treated with 0.9% NS nebulization. In the present study Mean ± SD age of the children in months is 6.83 ± 4.69, whereas the Mean ± SD in other studies (Lowell et al[14], Sarrell et a1[15] were 8.9 ± 5.8 & 12.5 ± 6 respectively).

The present study shows slight male preponderance (males 55.32% and females 44.76%) which is comparable to study by Sarrell et al[15] and Kuzik et al[19].In the present study 61% of cases with bronchiolitis presented between November to February, which is comparable to the study done by Cherian T et al[16], Weber MW et al[17].

In contrast more cases of bronchiolitis were presented between December to April in studies done by Sarrell et al[15], Mandelberg et al[18], probably due to variation in geographical distribution and climatic conditions.

In the present study the base line CSS of 3% hypertonic saline group and 0.9% saline group were 10.36 ± 0.62, 10.33 ± 0.64 respectively (p = 0.81).

Table No –8 Comparison Of Post Intervention Clinical Severity Score Between The Groups On Day 1

Authors & No. of Cases	Cases treated with 3% HTS nebulization Mean ± SD	Cases treated with 0.9% NS nebulizationMean ± SD	Mean Difference (95% CI)	P value
Sarrell et al[15] N = 65	4.36 ± 1.05	5.64 ± 1.54	- 1.28(-1.92 to -0.64)	0.0001
Mandelberg et al[18] N = 93	7.7 ± 1.54	7.81 ± 1.49	-0.11(-0.93 to -0.71)	0.03
Guy Tal et al[20] N = 42	6.25 ± 1.1	7 ± 1	-0.75 (-1.39 to -0.11)	0.03
Present study N= 105	7.11 ± 0.78	8.21 ± 0.75	-1.09(-0.83 to -1.39)	0.02

In the present study at the end of the day (Day 1), cases treated with 3% HTS nebulization had a significant lower Clinical Severity Score (CSS) compared to 0.9% NS group with a mean difference of -1.09 (-0.83 to -1.39).This shows a reduction of 13.3% in 3 % HTS group compared to 0.9% NS group.The decrease in CSS score at the end of day 1 in 3% HTS group when compared to 0.9% NS group is similar to the study of Sarrell et al[15], Mandelberg et al[18] and Guy Tal et al[20].

Table No – 9 Comparison Of Post Inhalation Clinical Severity Score Between The Groups On Day 2

Authors& No. of Cases	Cases treated with 3% HTS nebulization Mean ± SD	Cases treated with 0.9% NS nebulization Mean ± SD	Mean Difference (95% CI)	P value
Sarrell et al[15] N = 65	2.77 ± 1.4	4.77 ± 2.31	-2.0 (-2.93 to -1.07)	0.001
Mandelberg et al[18] N = 93	6.41 ± 1.4	6.92 ± 1.62	-0.51(-1.36 to -0.34)	0.003
Guy Tal et al[20] N = 42	5.35 ± 1.3	6.45 ± 1	-1.10 (-1.81 to -0.39)	0.003
Present study N = 105	4.42 ± 0.69	5.48 ± 0.85	-1.07 (-0.76 to -1.36)	0.001

In the present study at the end of the day (Day 2), cases treated with 3% HTS nebulization had a significant lower Clinical Severity Score (CSS) compared to 0.9% NS group with a mean difference of -1.07 (-0.76 to -1.36).This shows a reduction of 19.4% in 3 % HTS group compared to 0.9% NS group. In the present study the decrease in the CSS score at the end of day 2, in 3% HTS group when compared to 0.9% NS group, is similar to study of Sarrell et al[15], Mandelberg et al[18] and Guy Tal et al[20].

Authors & No. of Cases	Cases treated with 3% HTS nebulization Mean ± SD	Cases treated with 0.9% NS nebulization Mean ± SD	Mean Difference (95% CI)	P value
Sarrell et al[15] N = 65	1.77 ± 2.4	4.41 ± 2.57	-2.64 (-3.85 to -1.43)	0.001
Mandelberg et al[18] N = 93	5.81 ± 1.68	6.08 ± 2.03	-0.27 (-1.37 to 0.83)	0.008
Guy Tal et a[20] N= 42	4.7 ± 1.5	5.72 ± 1	-1.02 (-1.99 to -0.05)	0.008
Present study N = 105	2.17 ± 0.38	4.27 ± 0.49	-2.09 (-2.26 to -1.93)	0.01

Table No – 10 Comparison Of Post Inhalation Clinical Severity Score Between The Groups On Day – 3

In the present study at the end of the day (Day 3), 3% HTS group had a significant lower Clinical Severity Score (CSS) compared to 0.9% NS group with a mean difference of -2.09 (-2.26 to -1.93). This shows a reduction of 48.3% in 3 % HTS group compared to 0.9% NS group.In the present study the decrease in the CSS score on day 3 in 3% HTS group when compared to 0.9% NS group is similar to study of Sarrell et al[15], Mandelberg et a1[18] and Guy Tal et al[20].

With the ongoing treatment, the CSS score at the end of day 1 in 3% HTS group and 0.9% NS group were 7.11± 0.78 & 8.21 ± 0.75 respectively, which significantly lowered to 2.17 ± 0.38 & 4.27 ± 0.49 by the end of day 3. This difference in CSS scores represents reduction of 75% in 3% HTS group and 50% in 0.9%NS group.The time for resolution of signs and symptoms were reduced with significant mean difference of -16.37(-13.53 to -19.21) hours in 3% HTS group compared to 0.9% NS group.The duration of hospital stay was decreased by 1 day (25% reduction), in 3% HTS group compared to 0.9% NS group and no adverse effects were noted with the use of 3% hypertonic saline nebulization.

Table No – 11 Comparison Of Outcome Parameter Duration Of Hospital Stay In Both The Groups

Authors & No. of Cases	Duration of hospital stay in days		Mean Difference (95% CI)	P value
	Cases treated with 3% HTS nebulization Mean ± SD	Cases treated with 0.9% NS nebulization Mean ± SD		
Kuzik et al[19] N= 96	2.6 ± 1.9	3.5 ± 2.9	-0.94 (-1.48 to -0.40)	0.0006
Mandelberg et al[18] N=93	3.01 ± 1.2	4.02 ± 1.9	-1.01 (-1.34 to – 0.82)	0.05
Guy Tal et al[20] N= 42	2.6 ± 1.4	3.5 ± 1.7	-0.9 (-1.38 to -0.44)	0.02
Present study N=105	3.06 ± 0.23	4.10 ± 0.36	-1.04(-0.92 to -1.15)	0.001

In the present study the duration of hospital stay in cases treated with 3% HTS nebulization was decreased by one day which is comparable to studies done by Kuzik et al[19], Mandelberg et al[18], and Guy tal et al[20A].Our study shows that 3% HTS may be effective in treating bronchiolitis in children hospitalized with bronchiolitis.

VI. Conclusions

The duration of hospital stay in cases treated with 3% HTS group was decreased by one day, compared to 0.9% NS group and this shows 25% reduction in the mean duration of hospital stay, among children hospitalized with bronchiolitis. Nebulized 3% HTS appears to be safe, without adverse effects and promises a potential benefit for treatment of bronchiolitis in children.

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