Original Research Paper

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Pediatrics

Hypertonic Saline nebulization in the Viral Bronchiolitis in Infants at Tertiary care center, Bhagalpur

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ABSTRACT

Objective To investigate the use of nebulized 3% hypertonic saline (HS) for treating viral bronchiolitis in moderately ill hospitalized infants by a prospective, randomized, double-blinded, controlled, multicenter trial.

Study design A total of 96 infants (mean age, 4.7 months; range, 0.3 to 18 months) admitted to the hospital for treatment of viral bronchiolitis were recruited from Jawaharlal Nehru medical college & hospital during bronchiolitis seasons (november 2015to marchy 2016). Patients were randomized to receive, in a double-blind fashion, repeated doses of nebulized 3% HS (treatment group) or 0.9% normal saline (NS; control group), in addition to routine therapy ordered by the attending physician. The principal outcome measure was hospital length of stay (LOS).

Results On an intention-to-treat basis, the infants in the HS group had a clinically relevant 26% reduction in LOS to 2.6to 1.9 days, compared with 3.5 to 2.9 days in the NS group (P .05). The treatment was well tolerated, with no adverse effects attributable to the use of HS.

Conclusions The use of nebulized 3% HS is a safe, inexpensive, and effective treatment for infants hospitalized with moderately severe viral bronchiolitis.

KEYWORDS :

Respiratory syncytial virus (RSV) accounts for the majority of viral bronchiolitis cases, although other viruses including human metapneumovirus, adenovirus, parainfluenza, rhinovirus, and influenza,.[1-3] Given that virtually all children become infected with RSV by age 2 years and that at least 1% of these children will develop bronchiolitis sufficient to require hospitalization,the burden of this disease is high, accounting for up to 17% of all infant hospitalizations, Despite the high prevalence and morbidity of bronchiolitis, therapy remains con- troversial and without widely accepted therapeutic guidelines other than supportive-care. Bronchiolitis is characterized by airway plugging with sloughed epithelium, rmucus, and edema rather than bronchospasm. Nevertheless, the use of nebulized bronchodilators continues to be common,despite extensive evidence supported by 3- meta-analyses that the benefits are limited, short term, and do not justify routine use. Similarly, although steroids might reasonably be expected to decrease the inflammatory response in bronchiolitis, published data are conflicting, with equally well-designed studiesconcluding that steroidsmay be either effectiveor ineffective. The, primary treatment, therefore, remains largely supportive, with administration of fluids andh supplemental oxygen, observation, and mechanical ventilatory support as needed.

Several reports over the last decade have demonstrated that inhalation of nebulized 6% to 10% hypertonic saline (HS) improves both immediate and long-term clearance of. small airways in patients with cystic fibrosis. The exact mechanism is unknown but lis thought to facilitate removal of inspissated mucus through osmotic hydration, disrup-tion of mucus strand cross-linking, and reduction of mucosal edema.In otherwise,

ANOVA	Analysis of variance
RDAI	Respiratory Distress Assessment Instrument
HS	Hypertonic saline
RSV	Respiratory syncytial virus
SaO_2	Oxygen saturation

healthy infants hospitalized with viral bronchiolitis, the reg-ular administration of nebulized 3% HS combined with epi-nephrine decreased length of stay (LOS) by approximately 22% compared with infants receiving the same dose of epi-nephrine mixed in 0.9% normal saline (NS).[29] Similarly, in ambulatory infants with mild bronchiolitis, inhalation of neb-ulized 3% HS (with terbutaline) improved clinical scores but did not produce a decrease in hospital admission rate.[30] Both of the aforementioned studies used 3 times per day dosing, which is significantly less than the 3 to 6 times per hour regimens often used to deliver nebulized medication to chil-dren in respiratory distress.[31-33]

The purpose of the present study was to investigate the addition of frequently nebulized 3% HS to standard therapy of moderately ill infants hospitalized with typical viral bron-chiolitis in a prospective, randomized, double-blind, con-trolled fashion. The primary objective was to compare the LOS of these infants with that of a control group of infants receiving standard therapy plus frequently nebulized NS.

METHODS

Patients

Infants up to age 18 months who were admitted to the hospital for the treatment of moderately severe viral bronchi-olitis were eligible for study. The diagnosis of moderately severe bronchiolitis required a history of a preceding viral upper respiratory infection, the presence of wheezing or crackles on chest auscultation, plus either an oxygen satura-tion (SaO_2) of 94% in room air or significant respiratory distress as measured by a Respiratory Distress Assessment Instrument (RDAI)[34] score . In brief, 6 separate assess-ments of retractions and auscultatory findings are made and assigned a numerical score; the sum of these scores provides the RDAI score ranging from 0 to 17, with increasing scores indicating increasing respiratory distress.

Exclusion criteria included a history of any of the fol-lowing: previous episode of wheezing, chronic cardiopulmo-nary disease or immunodeficiency; critical illness at presenta-tion requiring admission to intensive care; the use of nebulized HS within the previous 12 hours; or premature birth (gestational age # 34 weeks).

Setting

The study was conducted at Jawaharlal Nehru medical college and hospital, Data were collected during the winter bronchiolitis seasons between November 2015 and march 2016.

Study Design

Patients admitted to hospital with bronchiolitis were assessed within 12 hours for entry into the study. If inclusion/ exclusion criteria were satisfied, then informed consent was obtained, and the patient was randomized to receive treat-ment with 4 mL of nebulized study solution containing either 3% HS (study group) or NS (control group). The study solution was administered in a double-blind fashion every 2 hours for 3 doses, followed by every 4 hours for 5 doses, followed by every 6 hours until discharge. After study enroll-ment, any additional (nonprotocol) treatments were at the sole discretion of the attending physician, who was blinded to the study treatment. If additional treatments included nebu-lized medication, the medication was nebulized in 4 mL of the assigned study solution (ie, HS or NS). All inhaled therapies were delivered to a settled infant from a standard oxygen-driven hospital nebulizer through a tight-fitting face-mask, or head box, whichever was better tolerated by the infant.

Patients were randomized independently at each study site to receive either HS or NS using a computer-based randomization program. Study solutions were prepared by a research pharmacist and were identical in appearance and odor. The identity of the study solutions was blinded to all participants, care providers, and investigators. Clinical re-sponse was determined by the designated study physician using RDAI scores and SaO_2 readings at study entry and then at least once daily.

Determination of LOS

LOS was defined as the time between study entry (within 12 hours of admission to the hospital) and the time at which the infant either reached protocol-defined discharge criteria as measured by the study physician or was discharged from the hospital on independent clinical grounds by the attending physician, whichever came first. Protocol-defined discharge criteria required both an RDAI score 4 and an SaO_2 of at least 95% in room air for 4 hours.

Ethics

The study was approved by the ethics and human research committees of the hospitla. In-formed written consent was obtained from at least 1 parent of each infant before enrollment.

Statistical Strategy

A reduction in LOS of 1 day was previously proposed as being clinically significant[32] and was adopted in this study. It was anticipated that this would require a sample size of approximately 46 patients per trial arm, for 80% power, to show a *P* value # .05. This number is based on a prestudy mean LOS at the largest study hospital of 4.1 1.7 days (unpublished data). Data were entered into an Excel spreadsheet (Microsoft Corp, Redmond, WA) and imported into SPSS version 12.0.1 software (SPSS Inc, Chicago, IL)

Table I. Patient demographics and illness status at baseline

	HS	NS	
	(n 47)*	(n 49)*	P
% male	57%	61%	.84
Age (months)	4.4 3.7	4.6 4.7	.54
Duration of illness before	4.5 2.3	4.0 2.4	.30
admission (days)			
Respiratory distress	7.8 2.5	8.1 3.3	.69
clinical score			
% SaO2 in room air	94.9 3.9	95.2 3.4	.71
Infants treated with	37 (86%)	41 (91%)	.52
bronchodilator before			
study entry (%)			
Infants treated with	1 (2.5%)	1 (2.4%)	1.0
systemic steroids			
before study entry (%)			
Infants treated with	6 (15%)	4 (9.8%)	.52
antibiotics before study			
entry (%)			
Infants tested for RSV	40	40	1.0
RSV positive (%)	25 (62%)	30 (75%)	.39

*Sample sizes vary slightly for the individual comparisons due to missing data.

for analysis on an intention-to-treat basis. Descriptive analy-ses were completed overall and also for the control and study groups separately. The x^2 test (Fisher's exact) was used to examine the association between categorical variables and group, and independent sample *t* tests and Levene's test for equality of variance were used to assess the association be-tween numeric variables and group. One-way analysis of variance (ANOVA) was used to compare data from the 3 study sites. To test for the potential effect of age on the results, the patients were divided into 3 age groups (0 to 6 months, 7 to 12 months, and 13 to 18 months), and the effects of age and treatment were tested in a 2-way ANOVA.

RESULTS

Study Population

A total of 96 previously well infants (mean age, 4.7 4.2 months; range, 10 days to 18 months) with viral bron-chiolitis were enrolled during the bronchiolitis seasons from November 2015 to March 2016. Forty-seven infants were randomized to the HS treatment group, and 49 were randomized to the NS control group. Five infants (2 from the HS group and 3 from the NS group) were withdrawn at parental request before study completion but were included in the final intention-to-treat analysis.

The HS and NS groups were comparable at baseline and typically presented on the fifth day of illness (range, 1 to 14 days) with borderline hypoxia (mean SaO_2, 95%; range, 85% to 100%) and moderate respiratory distress (mean clinical score, 8 out of 17; range, 4 to 17) (Table I). Some 69% of all

Table III. Treatments received during the study

	HS		NS		P
Treatment	(n 47)*		(n 49)*		
Study solution alone	3.2	3.0	3.8	4.1	.46
(nebulizations/day)					
Albuterol study solution	3.1	3.5	3.6	3.6	.49
(nebulizations/day)					
Racemic epinephrine study	2.7	3.7	1.6	2.4	.13
solution (nebulizations/day)					
Steroids study solution	0.39	0.83	0.26	0.60	.42
(nebulizations/day)					
Total nebulizations/day	9.1	3.0	9.2	4.5	.93
Number of patients given any	8 (17%)		7 (14%)		.78
systemic steroid (%)					
Number of patients given any	5 (11%)		10 (20%)		.26
antibiotic (%)					

*Sample sizes vary slightly for the individual comparisons due to missing data.

tested infants were positive for RSV. Subset comparison of the SKMC and Canadian sites revealed minimal differences at baseline (Table II; available at www.jpeds.com). Although the Arab infants tended to be sicker (RDAI 8.9 2.9 vs 6.2 1.9; *P* .001) and more likely to receive previous treatment with a bronchodilator (98% vs 70%; *P* .001), all other measurements were comparable.

Treatment Received

After enrollment, all treatments (protocol and add-on) received by infants in the HS and NS groups were comparable (Table III). The infants received a mean of 9 nebulizations of study solution per day delivered alone (38% of treatments) or co-administered with albuterol (salbutamol; 37%), racemic epinephrine (racepinephrine; 23%), or inhaled steroid (3%). Subset comparison of the SKMC and Canadian sites revealed minimal differences in the treatments received (Table IV; available at www.jpeds.com). Treatment at SKMC was more likely to include antibiotics (*P* .002) as well as the addition of racemic epinephrine to the inhaled study solution (*P* .003).

Adverse Effects of HS

All participants tolerated therapy without apparent ad-verse effects and were eventually discharged after achieving full recovery. No infants were withdrawn by the medical staff due to clinical deterioration or the need for intensive care support. Although 5 infants were withdrawn at parents' re-quest because of perceived adverse effects of therapy, only 2 of these infants were receiving HS. One of these infants (a 2-month-old male) cried very vigorously during his third inhalation (HS alone) and again with his fifth inhalation (HS with racemic epinephrine) and was withdrawn at that time. This was not associated with any significant acute change in his clinical condition, and he was eventually discharged on day 6. The second infant (a 3-month-old female) was with-drawn because of agitation after her second inhalation (HS 268Kuzik et alThe Journal of Pediatrics September 2007

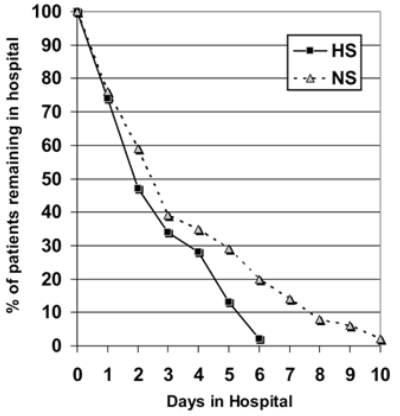

Figure. Percentage of patients in each group remaining in the hospital. with albuterol), which was not associated with a significant change in her respiratory status. She was eventually dis-charged on day 2.

Response to Therapy

The endpoint of LOS was identified by the attending physician using clinical grounds alone (45% of patients) or by reaching protocol-established discharge criteria as measured by the study physician (55% of patients), whichever came first. One-way ANOVA confirmed that the LOS did not differ significantly between study sites for either the NS group (*P*.12) or the HS group (*P*.44).

Infants in the control group had a mean LOS of 3.5 2.9 days, whereas infants treated with nebulized 3% HS were discharged on average 1 day sooner, with a 26% reduction in LOS to 2.6 1.9 days (*P* .05). There was a trend toward greater improvement in infants under age 6 months, but this difference did not attain statistical significance (*P* .17). The percentage of patients from each group remaining in hospital each day is shown in the .

DISCUSSION

This study demonstrates that inhaled 3% HS is an effective treatment for infants up to age 18 months hospital-ized with viral bronchiolitis. Repeated inhalations of nebu-lized HS reduced the LOS by approximately 1 day, from 3.5 2.9 to 2.6 1.9 days. This is a clinically relevant benefit with the potential for widespread impact on the treatment of bronchiolitis.

The infants that we studied came from a population that was geographically and ethnically very diverse. Neverthe-less, these infants were very similar to those described in other bronchiolitis studies, with a slight male predominance (62%), primary infection with RSV (69%), mean age of 4.7 months, and LOS in the control group of 3.5 to 4 days.[7,35,36] Strict inclusion and discharge criteria were used to minimize pos-sible confounding effects of uncharacterized and evolving wheezing phenotypes and to minimize between-site variability. The clinical scoring system chosen has been widely used in other studies on bronchiolitisand has been proposed to be the scoring system of choice for further studies.[15] Therefore, our findings should be universally applicable to other previously healthy infants hospitalized with moderately severe viral bronchiolitis.

The majority of our patients received bronchodilators before study entry. In addition, although our study protocol did not require or encourage the co-administration of bron-chodilator with the study solution, blinded attending physi-cians prescribed bronchodilators approximately 5 times per day. This finding was not unexpected, because the use of bronchodilators in bronchiolitis remains widespread, with some reporting it in more than 80% of patients.[11,12] It is also possible that attending physicians prescribed bronchodilators to prevent possible adverse effects of HS. Although inhalation of HS may cause bronchoconstriction in asthmatics,[38] and co-administration with a bronchodilator is often recom-mended,[24,39] others have reported that inhalation of 4.5% to 7% HS (without a bronchodilator) can be performed safely in healthy nonasthmatic children[40,41] or in children with mod-erately severe small airway obstruction secondary to cystic fibrosis.[42] In our study, there were no apparent adverse effects attributable to the use of HS without a bronchodilator, al-though the numbers were insufficient to allow further explo-ration of this issue. However, there was no increase in add-on bronchodilator therapy in the treatment group, suggesting that the use of HS in this setting was not associated with a clinically significant increase in lower airway obstruction.

The use of inhaled HS in the treatment of viral bron-chiolitis in hospitalized infants is a novel therapy that was first reported in 2003[39] and recently strengthened with the pub-lication of a 2-year extension of the original study.[29] These authors demonstrated that 3 times a day dosing with 4 mL of 3% HS containing 1.5 mg of epinephrine compared with the same dose of epinephrine in NS reduced the LOS from 3.6 1.6 days to 2.8 1.3 days, a 22% improvement (*P* .05). They included epinephrine to prevent possible adverse effects of HS and attributed the beneficial effects in the treatment group to the presence of HS. Our study was very similar but differed primarily in the inclusion of slightly older infants (up to age 18 months), plus the much more frequent dosing of HS (9.1 3.0 inhalations/day). In our hands, increasing the frequency of inhaled HS produced a further reduction in the LOS to 26%, but this reduction was not significant compared with 3 times a day dosing.

The routine use of 3% HS in the treatment of infants hospitalized with bronchiolitis has the potential for enormous economic benefit. A 26% reduction in LOS not only will return infants to home and their parents to work a day sooner, includes the widespread use of bronchodilators nebulized with NS,[11,12] exceed $580 million per year.[6,43] Therefore, the substitution of NS with the comparably priced 3% HS, with the subsequent reduction in LOS, has the potential to save the US healthcare system more than $150 million annually.

In summary, inhaled 3% HS is a safe, inexpensive, and effective treatment for previously well infants admitted to the hospital with moderately severe viral bronchiolitis. Further research is needed to determine the optimum dosing and to identify whether there is any benefit from co-administered bronchodilator.

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