A randomized, controlled trial of nebulized 5% hypertonic saline and mixed 5% hypertonic saline with epinephrine in bronchiolitis.

Etude randomisée en double aveugle de la nébulisation de sérum salé hypertonique 5%, de mélange de sérum salé hypertonique 5% et d'adrénaline dans la bronchiolite.

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RÉSUMÉ

Prérequis: La bronchiolite aigue est un problème de santé publique en Tunisie. Le traitement reste un sujet de controverse. Il semblerait que les nébulisations de sérum salé hypertonique améliorent le score de sévérité de la bronchiolite et raccourcissent la durée du séjour

But: Evaluer l'efficacité de la nébulisation de sérum hypertonique à 5% seul ou en association avec l'adrénaline à 0.1% dans le traitement du premier épisode de bronchiolite aigue modérée

Méthodes : Etude prospective randomisée en double aveugle réalisée au service de médecine infantile B de l'hôpital d'enfants de Tunis Béchir Hamza entre février et mars 2013. Quatre-vingt-quatorze nourrissons ont été inclus dans l'étude et ont reçu au hasard soit des nébulisations de sérum physiologique, soit le sérum salé hypertonique à 5% soit un mélange de sérum salé hypertonique à 5% et d'adrénaline.

Résultats : Nous n'avons trouvé de différence significative dans le score de sévérité de Wang, la fréquence respiratoire, la saturation en oxygène à l'air ambiant et la fréquence cardiaque dans les trois groupes à T0, T30, T60, T120 min. Nous n'avons pas également noté de différence significative concernant la durée de l'hospitalisation entre les trois groupes
Aucun effet indésirable n'a été noté.

Conclusion : Les nébulisations de sérum salé hypertonique à 5% seul ou mélangé à l'adrénaline sont dénuées de risque mais ne semblent pas améliorer à court terme les nourrissons présentant un premier épisode de bronchiolite de sévérité modérée

Mots-clés
Bronchiolite ; épinephrine ; sérum salé hypertonique ; sifflements

SUMMARY

Background: Bronchiolitis is a public health problem in the word and in Tunisia. Nebulized hypertonic saline seems to have some benefits in bronchiolitis.

The aim of this study is to evaluate the efficacy of nebulized 5% hypertonic saline alone or mixed with epinephrine in bronchiolitis as measured by improvement in clinical score, oxygen saturation or reduction in duration of hospitalization.

Methods: This prospective, double blind, placebo controlled, randomized clinical trial was performed at Children's Hospital of Tunis from February 2012 to Mars 2012. A total of 94 patients less than 12 months of age with diagnosis of moderately severe bronchiolitis were enrolled and assigned to receive 5% nebulized hypertonic saline, mixed 5% hypertonic saline with standard epinephrine 0,1% or normal saline (placebo) at admission and every 4 hours during hospitalization.

Results: There were no significant difference between nebulized 5% hypertonic saline, mixed 5% hypertonic saline with epinephrine or normal saline at baseline, T30 min, T60 min, and T120 min after start study in Wang severity score, oxygen saturation in room air, rate respiratory and heart rate. There was no difference in duration of hospitalization.

Conclusion: Nebulized 5% hypertonic saline or mixed 5% hypertonic saline with epinephrine are safety but does not appear effective in treating moderately ill infants with the first acute bronchiolitis.

Key-words
Bronchiolitis; epinephrine; infant; hypertonic saline; wheezing

Acute bronchiolitis is the most common lower respiratory tract infection affecting children younger than 1 year (1). Bronchiolitis associated hospitalizations have increased considerably since 1980 becoming a public health problem in the world and in Tunisia (2). Despite the high prevalence and morbidity of bronchiolitis, therapy remains controversial. Metaanalyses of data on the most-used therapies, namely, nebulized albuterol and epinephrine, failed to demonstrate any effect on relevant clinical outcomes (3-8). Current clinical practice guidelines do not recommend the routine use of any medication for bronchiolitis (9). Despite the evidence, use of ineffective therapies for bronchiolitis remains high (10-12).

Respiratory syncytial virus (RSV) is the most important pathogen responsible for acute bronchiolitis. Pathophysiologically, bronchiolitis is an infection of the bronchiolar epithelium, with subsequent profound submucosal and adventitial edema, increased secretion of mucus, peribronchiolar mononuclear infiltration, and epithelial cell necrosis. These changes obstruct flow in the small airways, leading to hyperinflation, atelectasis, and wheezing (13-15).

Several recent reports have found that inhalation of nebulized 3% hypertonic saline (HS) improves both immediate and long-term clearance of small airways in children with viral bronchiolitis (16-19). The exact mechanism of action is unknown, but HS is thought to facilitate removal of inspissated mucus through osmotic hydration, disruption of mucus strand cross-linking and reduction of mucosal edema(20-21).

In all studies to date, HS has been coadministered with a bronchodilator to reduce the theoretical risk of HS-induced bronchospasm; only one study suggests that higher concentrations of hypertonic saline 5% mixed with epinephrine can be safely used to treat bronchiolitis in the hospital setting.

The objective of this study was to evaluate the efficacy and the safety of nebulized 5% hypertonic saline alone or mixed with standard epinephrine 0,1% in moderate severity bronchiolitis as evidenced by improvement in oxygen saturation in room air, reduction in the Wang severity score (22), respiratory rate and the hospital stay duration.

To our knowledge, no study to date has examined the role of 5% hypertonic saline alone for the treatment of bronchiolitis in hospitalized patients. This is also the first study to investigate the risk of bronchospasm or other significant adverse effects with 5% hypertonic saline solution administered without bronchodilators for viral bronchiolitis.

METHODS

Design

This prospective, double blind, placebo-controlled, randomized clinical trial was performed from February 2012 to Mars 2012 at the department of pediatrics B of the Children's Hospital of Tunis (Tunisia)

Patients

Eligible infants included all previously well infants aged between one month old and 12 months old with a clinical diagnosis of first acute viral bronchiolitis and who are hospitalized during the study period. Viral bronchiolitis is defined as an acute infection of the lower respiratory track, preceded by or accompanied by fever and/or rhinitis, and characterized by expiratory wheezing and increased respiratory effort. Moderate severity bronchiolitis is characterized by a Wang severity score 3. The Wang score is based on two respiratory variables, wheezing and retraction and general condition. This score was chosen because of its face validity, high inter-and intra reliability and its discriminative ability. Children were excluded from the study if they had a gestational age at birth <34 weeks, or underlying chronic cardiac or pulmonary disease (eg, bronchopulmonary dysplasia, cystic fibrosis), recurrent wheezing, severe respiratory distress, as evidence by apnea, heart rate> 200 beats per minute, respiratory rate >80 breath/minute, profound lethargy, duration of illness exceeding 15 days.

Study design

After an initial clinical assessment, patients were randomly assigned, by means of a computer-generated table of random numbers, to receive blinded treatment with either nebulized 5% hypertonic saline (4ml), or mixed 5% hypertonic saline with standard epinephrine (2ml standard epinephrine + 2 ml 5% hypersaline) or normal saline placebo (4ml of normal saline). A medical doctor blinded to patient assignment prepared each morning solutions which were similar in appearance and smell, stored in identical syringes, labeled only by a code number. Nebulizations were administrated for 10 minutes with small, tight-fitting plastic face mask with an up draft nebulizer with continuous flow of 100% oxygen at 6 to 7 L/min. Infants received nebulizations every 4 hours during the study period. All infants with oxygen saturation in room air of 93% or less received supplemental oxygen when not receiving nebulizations. All patients were evaluated using standardized complete respiratory history and physical examination by the medical doctor. Initial history included age, gender, duration of the illness, current medications, allergies, family history of wheezing or smoking, birth history, history of previous chronic illness, cardiac or pulmonary disease. All patients had a baseline clinical assessment consisting of the wang severity score, respiratory rate, heart rate and pulse oximetry. The assessment were made by medical doctor who is blind for the solution nebulized, when the infant was relatively calm and had breathing room air for at least 10 minutes. The clinical assessment was repeated 30, 60, 120 minutes after the start of the first treatment. An additional secondary outcome measure was hospital stay duration. Criteria of discharge from the hospital included: no need for supplemental oxygen, Wang severity score less than 3 and adequate fluid intake.

This study was approved by the Human Ethics committee of the Charles Nicolle's hospital, because we have not a Human Ethics committee in our hospital and the Tunisian legislation provides that in such cases it is allowed to submit the study to the human Ethics committee of the institution closest.

Statistical analysis

The following data were analyzed using SPSS/PC V 11.5 soft ware.

For descriptive statistics we calculated proportions for qualitative variables and means with standards derivation and IC 95% for quantitative variables.

We used parametric t-test or non parametric Mann and Withney test for comparison of two means from independent groups. We used Wilcoxon test for comparison of two means from dependant groups. We used X2 or Ficher's exact test for comparison of two proportions

from independent groups. A value of P 0.05 was taken as indicating statistical significance.

RESULTS

97 infants were randomized to the study protocol. Two patients were withdrawn by the pediatric inpatient team because of worsening clinical status during the first 24 hours. These patients had been randomized to receive placebo. Another patient was withdrawn at parents' request because the parents refused the hospitalization. These three patients were excluded from the statistical analysis. 94 patients achieved the study.

Twenty six patients received normal saline (placebo) (G1), 31 patients received 5% hypertonic saline (G2) and 36 a mixed 5% hypertonic saline and standard epinephrine (G3). The three groups were similar for all baseline variables (Table I).

Table 1 : Baseline characteristics of enrolled infants

	G1	G2	G3	p
Mean Age (SD)	3,06±2,47	3,76±2,8	3,28±2,53	0,57
Male/female	14/12	22/9	22/15	0,39
Familial atopy	6/14	3/18	4/26	0,279
Duration of symptoms before enrollment, (days)	3,58±1,86	4,48±2,23	4,20±3,41	0,54
Baseline severity score	4,28±1 ;53	5,35±1,4	5,76±1,84	0,11
Respiratory rate	60,27±12,5	57,74±14,02	61,73±10, 32	0,40
Baseline O2 saturation, %	95,22±2,2	94,2±6,29	94,76±4,1	0,66
Heart rate	125, 35±14,7	133,8±15,94	130,8±18,5	0,16

There was no significant difference in mean severity score between the three groups at any time point (T0, T30, T60, T 120) (Table II);

At 120 min after nebulisation, the mean severity score in G3 was reduced from baseline by 31,609% ±24,16 compared to 24,22% ± 21,76 in G2 and 23,18% ± 22,03 in G1 without significant difference (p=0,269) (figure 1).

Figure 1: The decrease of clinical severity scores in the groups from baseline to 120 min

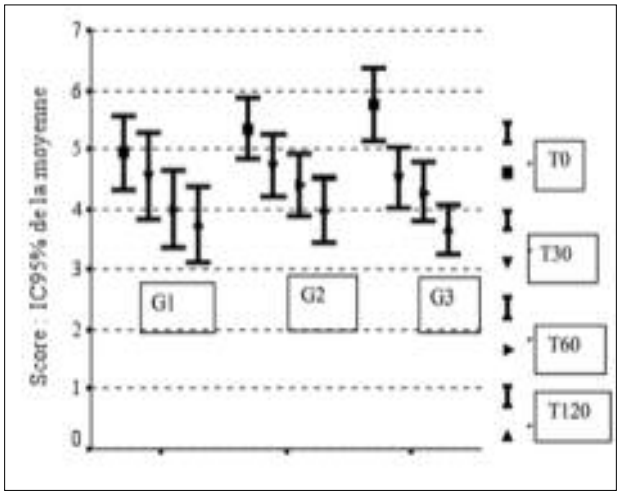

Table 2 : Clinical severity scores in the groups

	G1 normal saline	G2 5% hypertonic saline	G3 mixed 5% hypertonic saline with epinephrine	P
T30	4,42±1,8	4,74±1,3	4,54±1,53	0,74
T60	4 ± 1,55	4,42±1,4	4,3±1,45	0,557
T120	3,76±1,562	4±1,483	3,68±1,248	0,633

There was no significant difference in mean of oxygen saturation in room air or respiratory rate between the three groups at any time point (T0, T30, T60, T 120)$; No patients in either treatment group experienced clinically significant adverse side effects (tachycardia, flushing, tremor or bronchospasm)

The mean time for discharge was 3,5±1,973 j in G3; 3,6± 1,7 j in G2 and 4,48±3,81 j in G1 without significant difference (p=0,316).

DISCUSSION

The analysis of the outcome measures in this randomized trial show no clear benefit to nebulized 5% hypertonic saline solution or mixed 5% hypertonic saline with standard epinephrine 0,1% in hospitalized patients with moderate severity bronchiolitis, as evidenced by improvement in oxygen saturation in room air, severity score, respiratory rate at any time point or duration of hospital stay.

To the best of our knowledge, this is the first study examining the role of 5% hypertonic saline alone for the treatment of bronchiolitis in hospitalized patients. It is also the first to address directly the adverse effect profile of 5% hypertonic saline solution, used without bronchodilators, in bronchiolitis. In this study no significant adverse effects was observed with nebulized 5% hypertonic saline solution without bronchodilators.

To date, the majority of studies of nebulized hypertonic saline in bronchiolitis used 3% hypertonic saline. The recent Cochrane systematic review (13) included four methodologically acceptable randomised controlled trials (RCT) among 254 infants less than two years old, with a clinical diagnosis of bronchiolitis. This review showed that hypertonic saline nebulization resulted in shorter duration of hospitalization among admitted infants, and better clinical score among non-admitted infants, although it failed to reduce the rate of hospitalization among them. No adverse events were reported. The authors concluded that nebulized 3% hypertonic saline is a clinically useful intervention in infants with bronchiolitis.

This systematic review was strongly critiqued by Mathew who stipulated that limited data and limited number of subjects, non-superiority of hypertonic saline in terms of clinical score among admitted infants, failure to reduce hospitalization rate among outpatient infants and combining the data of inpatients with outpatients does not allow such conclusions (23).

Only one trial evaluated the efficacy and the safety of nebulized 5% and 3% hypertonic saline in bronchiolitis (24). The nebulization was mixed with 1,5 ml of racemic epinephrine in a double-blinded fashion on enrollment and every 4 hours thereafter until the patients were ready for discharge. The authors concluded that nebulization with 5% hypertonic proved superior to 0.9% saline for improving the bronchiolitis severity score in patients with viral bronchiolitis in the

early treatment setting, and possibly superior to 3% saline. However, the relatively small number of patients enrolled does not allow them to distinguish the efficacy of 3% saline and 5% saline in a definitive way. Our study is limited by the sample size which is not large. The lack of efficacy of nebulized 5% hypertonic saline or mixed 5% hypertonic saline with epinephrine in this study may be explained by this limitation. A larger study with standardized clinical scores, outcome measures, and long follow-up periods are now required to determine whether these trends arise from a clinically relevant treatment effect.

CONCLUSION

In summary nebulized 5% hypertonic saline or mixed 5% hypertonic saline with epinephrine does not appear to enhance recovery in this group of hospitalized infant with acute first bronchiolitis. Nebulized 5% hypertonic saline seems safety. This treatment merits further evaluation.

References

1. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986; 140: 543-546
2. Yorita KL, Holman RC, Sejvar JJ, Steiner CA, Schonberger LB. Infectious disease hospitalizations among infants in the United States. Pediatrics 2008;121:244 –252
3. Kellner JD, Ohlsson A, Gadomski AM, Wang EE. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. Arch Pediatr Adolesc Med 1996;150:1166 –1172
4. Flores G, Horwitz RI. Efficacy of 2-agonists in bronchiolitis: a reappraisal and metaanalysis. Pediatrics 1997;100:233-9
5. Gadomski AM, Bhasale AL. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2010;12:1-35
6. Hartling L, Bialy LM, Vandermeer B, et al. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2011;6:1-136
7. Fernandes RM, Bialy LM, Vandermeer B, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev. 2010;10:1-169.
8. King VJ, Viswanathan M, Bordley WC, et al. Pharmacologic treatment of bronchiolitis in infants and children: a systematic review. Arch Pediatr Adolesc Med 2004; 158:127-37
9. American Academy of Pediatrics, Subcommittee on Diagnosis and Management of Bronchiolitis. Clinical practice guideline: diagnosis and management of bronchiolitis. Pediatrics 2006;118:1774 -1793
10. Willson DF, Horn SD, Hendley JO, Smout R, Gassaway J. Effect of practice variation on resource utilization in infants for viral lower respiratory illness. Pediatrics 2001; 108:851- 5
11. Landrigan CP, Conway PH, Stucky ER, Chiang VW, Ottolini MC. Variation in pediatric hospitalists' use of proven and unproven therapies: a study from the Pediatric Research in Inpatient Settings (PRIS) Network. J Hosp Med 2008;3:292-8
12. Menif K, Kechaou W, Bouziri A et al. Current management of acute bronchiolitis in Tunisia. Tunis Med 2007;85: 65-8.
13. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001; 344:1917-28
14. Darville T, Yamauchi T. Respiratory syncytial virus. Pediatr Rev 1998; 19:55–61
15. Welliver JR, Welliver RC. Bronchiolitis. Pediatr Rev 1993; 14:134-9
16. Kuzik BA, Al Qadhi SA, Kent S, et al. Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. J Pediatr 2007;151:266-70.
17. Sarrell EM, Tal G, Witzling M, et al. Nebulized 3% hypertonic saline solution treatment in ambulatory children with viral bronchiolitis decreases symptoms. Chest 2002;122:2015-20.
18. Tal G, Cesar K, Oron A, et al. Hypertonic saline/epinephrine treatment in hospitalized infants with viral bronchiolitis reduces hospitalizations stay: 2 years experience. Isr Med Assoc J 2006;8:169-73.
19. Zhang L, Mendoza-Sassi RA, Wainwright C, et al. Nebulized hypertonic saline solution for acute bronchiolitis in infants. Cochrane Database Syst Rev 2008;4:1-36.
20. Robinson M, Hemming AL, Regnis JA, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. Thorax 1997;52:900-3.
21. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope 2000;110:1189-93.
22.. Wang EE, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. Am Rev Resp Dis 1992;145:106-9.
23. Mathew JL. Hypertonic saline nebulization for bronchiolitis. Indian Pediatr 2008; 45: 987-9
24. KAl-Ansari K, Sakran M, Davidson BL, et al. MDNebulized 5% or 3% Hypertonic or 0.9% Saline for Treating Acute Bronchiolitis in Infants. J Pediatr 2010;157:630-4