HYPERTONIC SALINE FOR INHALATIONS:

usage and clinical experience in cystic fibrosis and bronchiolitis
Nebulized hypertonic saline containing hyaluronic acid improves tolerability in patients with cystic fibrosis and lung disease compared with nebulized hypertonic saline alone: a prospective, randomized, double-blind, controlled study

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BACKGROUND

Hypertonic saline inhalation has been shown to be effective in patients with cystic fibrosis and lung disease. However, adverse events including marked airway narrowing are reported and a bronchodilator must be given before the administration of the product.

METHODS

We carried out a prospective, randomized, double-blind, parallel-group, controlled study of a hypertonic saline solution containing hyaluronic acid versus standard hypertonic saline therapy to assess whether the presence of hyaluronic acid would improve the tolerability of hypertonic saline.

RESULTS AND CONCLUSIONS

The results showed that nebulized was more effective in reducing the need for β(2) bronchodilators and caused a significant reduction in the incidence of adverse effects compared with nebulized hypertonic saline solution alone. Its safety profile indicates that can be used for the treatment of lung disease in cystic fibrosis.
Hyaluronic acid improves the tolerability of hypertonic saline in the chronic treatment of cystic fibrosis patients: a multicenter, randomized, controlled clinical trial

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TRIAL DESIGN AND METHODS

Between December 2009 and July 2011, four cystic fibrosis (CF) centers in Italy participated in a randomized, double-blind, controlled clinical trial to test whether 7% hypertonic saline (HS) administered together with 0.1% hyaluronic acid (HA) was better tolerated by patients who previously did not tolerate HS well on its own. Participants were CF patients at least 8 years old, in clinically stable conditions, with forced expiratory volume in 1 sec (FEV1) at least 50% predicted. Forty patients were recruited and randomized to receive either HS or HS plus HA (5 mL to be inhaled over 15 min, twice daily for 28 days). Primary endpoints were cough, throat irritation, salty taste, and overall acceptability, as assessed by each patient on a semiquantitative scale on a diary card. Secondary endpoint was FEV1 change at the end of treatment. Patients were randomized into randomly permuted blocks. The first and last doses were administered in hospital. In between, patients were treated at home. Patients, all caregivers, and the statistician who conducted the analysis (different from the one who generated the random list) were blinded to group assignment.

RESULTS

Severity of cough, throat irritation, and saltiness were more severe in patients treated with HS alone, both after the first inhalation and over the entire treatment period. Overall pleasantness was rated higher by patients treated with the combination product. All differences were highly significant. There were no changes in FEV1 between the first and last administrations. Five patients did not complete the study. Four patients (two from each group) withdrew because of cough or throat irritation. One more patient from the HS group withdrew because of a respiratory exacerbation at week 3.

CONCLUSIONS

HS is currently a cornerstone in the treatment of CF patients. The addition of HA to HS reduces the prevalence and severity of cough, throat irritation, and saltiness and may improve compliance in patients who previously did not tolerate HS well on its own. Longer-term studies could further assess the benefit of chronic treatment.
Inhaled hypertonic saline as a therapy for cystic fibrosis

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PURPOSE OF REVIEW
The beneficial effect of a short course of nebulized hypertonic saline on lung function for people with cystic fibrosis was first identified in 1996. At that time, competing hypotheses about the pathogenesis of cystic fibrosis lung disease predicted very different responses to long-term inhalation of hypertonic saline.

RECENT FINDINGS
Recent benchtop research supports the hypothesis that the liquid layer lining the airways is depleted in cystic fibrosis. In addition to osmotically restoring this liquid layer, hypertonic saline improves the rheological properties of the mucus and stimulates cough. The net result is accelerated mucus clearance that is short-lived for single doses but sustained with regular inhalation. Long-term use improves lung function mildly but has marked benefits with respect to exacerbations, quality of life and absenteeism, without promoting infection or inflammation.

SUMMARY
Hypertonic saline appears broadly applicable as an inexpensive therapy for most patients with cystic fibrosis.
Rationale for hypertonic saline therapy for cystic fibrosis lung disease

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ABSTRACT

Cystic fibrosis (CF) is caused by alterations in the CF transmembrane conductance regulator (CFTCR) gene. More than 1400 mutations in the CFTCR gene have been described, but the most common mutation (noted in 70% of CF chromosomes) is DeltaF508. Alterations in the CFTCR gene result in deranged sodium and chloride ion transport channels. This leads to failure of airway epithelia to hydrate their surfaces normally, particularly in response to infectious or toxic insults. Additional effects include mucus adhesion to airway surface, chronic inflammation, and infections. The concept that airway surface dehydration can cause CF-like lung disease is supported by in vitro data and in vivo animal models. Rehydrating airway surfaces may reduce or prevent lung injury and damage. Short- and longer term studies have shown that inhalation of hypertonic saline is well tolerated and improves lung function, reduces exacerbations, and improves quality of life in CF patients. This review discusses the importance of airway epithelial sodium and chloride channels in the pathogenesis of CF, and strategies (particularly the use of inhaled hypertonic saline) to reverse or minimize lung inflammation and injury in this disease.
The Efficacy and Tolerability of the Combination of Inhaled Hypertonic Saline and Hyaluronic Acid versus Inhaled Hypertonic Saline in Patients with Cystic Fibrosis

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BACKGROUND
Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease found among Caucasians. It is known to target many organs systems such as the lungs, liver, and intestines but the most affected organ is the respiratory tract. Patients with CF usually develop some type of pulmonary dysfunction resulting in frequent asthma-type exacerbations and chronic bacterial infections due to excessive mucus adhesion. Maintenance therapy with hypertonic saline (HS) has shown to be beneficial in helping with mucociliary clearance but compliance is low due to a high profile of side effects. Recent studies have shown that hyaluronic acid (HA) in addition to HS helps improve the tolerability of HS. The purpose of this review is to further evaluate the benefits of combination therapy on tolerability and efficacy in patients with CF.

METHODS
A comprehensive search of the medical literature was conducted using various search modalities including Medline/OVID, EBSCOhost/CINAHL, Web of Science, and Google scholar. Keywords used included: cystic fibrosis, hypertonic saline, and hyaluronic acid.

RESULTS
Three articles met the inclusion and exclusion criteria for this systematic review. All three articles were randomized control trials which showed a statistically significant improvement regarding tolerability with the addition of HA to HS.

CONCLUSION
This systematic review provides evidence that supports the indication for combination therapy with HA to improve tolerability and efficacy of HS therapy alone in patients with CF. However, these results would be strengthened with larger and longer randomized controlled studies.

KEYWORDS
cystic fibrosis; hypertonic saline; hyaluronic acid
Hyaluronic Acid Improves “Pleasantness” and Tolerability of Nebulized Hypertonic Saline in a Cohort of Patients with Cystic Fibrosis

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INTRODUCTION
Inhaled hypertonic saline improves lung function and decreases pulmonary exacerbations in people with cystic fibrosis. However, side effects such as cough, narrowing of airways and saltiness cause intolerance of the therapy in 8% of patients. The aim of our study was to compare the effect of an inhaled solution of hyaluronic acid and hypertonic saline with hypertonic solution alone on safety and tolerability.

METHODS
A total of 20 patients with cystic fibrosis aged 6 years and over received a single treatment regimen of 7% hypertonic saline solution or hypertonic solution with 0.1% hyaluronate for 2 days nonconsecutively after a washout period in an open crossover study. Cough, throat irritation, and salty taste were evaluated by a modified ordinal score for assessing tolerability; “pleasantness” was evaluated by a five-level, Likert-type scale. Forced expiratory volume in 1 second was registered before and after the end of the saline inhalations.

RESULTS
All 20 patients (nine males, 11 females, mean age 13 years, range 8.9-17.7) completed the study. The inhaled solution of 0.1% hyaluronic acid and hypertonic saline significantly improved tolerability and pleasantness compared to hypertonic saline alone. No major adverse effects were observed. No difference was documented in pulmonary function tests between the two treatments.

CONCLUSION
Hyaluronic acid combined with hypertonic saline solution may contribute to improved adherence to hypertonic saline therapy. Further clinical trials are needed to confirm our findings. Considering the extraordinary versatility of hyaluronic acid in biological reactions, perspective studies could define its applicability to halting progression of lung disease in cystic fibrosis.

KEYWORDS
cystic fibrosis; hyaluronic acid; hypertonic saline solution; pleasantness; tolerability
Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function

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ABSTRACT
Cystic fibrosis (CF) is a multisystem disorder with significantly shortened life expectancy. The major cause of mortality and morbidity is lung disease with increasing pulmonary exacerbations and decline in lung function predicting significantly poorer outcomes. The pathogenesis of lung disease in CF is characterised in part by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. This leads to accumulation of viscous mucus in the CF airway, providing an ideal environment for bacterial pathogens to grow and colonise, propagating airway inflammation in CF. The use of nebulised hypertonic saline (HTS) treatments has been shown to improve mucus clearance in CF and impact positively upon exacerbations, quality of life, and lung function. Several mechanisms of HTS likely improve outcome, resulting in clinically relevant enhancement in disease parameters related to increase in mucociliary clearance. There is increasing evidence to suggest that HTS is also beneficial through its anti-inflammatory properties and its ability to reduce bacterial activity and biofilm formation. This review will first describe the use of HTS in treatment of CF focusing on its efficacy and tolerability. The emphasis will then change to the potential benefits of aerosolized HTS for the attenuation of receptor mediated neutrophil functions, including down-regulation of oxidative burst activity, adhesion molecule expression, and the suppression of neutrophil degranulation of proteolytic enzymes.

KEYWORDS
cystic fibrosis; hypertonic saline; mucociliary clearance; neutrophils and inflammation
Seven percent hypertonic saline 0.1% hyaluronic acid in infants with mild-to-moderate bronchiolitis

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OBJECTIVES
Our study was aimed to evaluate the efficacy of 7% hypertonic saline and 0.1% hyaluronic acid (7% HS-HA) given by inhalation, in infants hospitalized for mild-to-moderate bronchiolitis.

METHODS
In a double-blind controlled study, 39 infants (23 boys) <7 months of age (median age 2 months) were enrolled and randomly assigned to receive either nebulized 7% HS-HA (7%NaCl + 0.1%HA) (n:21) or 0.9 normal saline (NS) (n:18) at a dose of 2.5 ml twice a day for 3 days. All infants were assigned a clinical severity score at admission and four times daily during hospitalization. Main outcome measures were number of days hospitalization, safety and daily reduction in the severity score.

RESULTS
No difference was found between the two groups for clinical severity score at admission. One child in the study group and two in the NS group interrupted the study protocol; 19% of infants in the study group and 11% in the NS group had mild cough after the aerosol. The length of stay in the control group and treatment groups were 4.8±1.5 versus 4.1±1.9 days, respectively (P = 0.09). There was a trend for shortening the hospitalization days in the treatment group by 14.6%. The use of NS in the control group was identified as an independent risk factor for length of hospital stay using the multivariate logistic regression model (P = 0.04). No difference was observed between the two groups for the clinical score reduction during the first 3 days hospitalization.

CONCLUSIONS
7% HS-HA is a safe and effective therapy in treating infants hospitalized for mild-to-moderate bronchiolitis.

KEYWORDS
7% hypertonic saline; bronchiolitis; hospital treatment; hyaluronic acid; therapy
Nebulised hypertonic saline solution for acute bronchiolitis in infants

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BACKGROUND
Airway oedema and mucus plugging are the predominant pathological features in infants with acute viral bronchiolitis. Nebulised hypertonic saline solution may reduce these pathological changes and decrease airway obstruction.

OBJECTIVES
To assess the effects of nebulised hypertonic (≥3%) saline solution in infants with acute viral bronchiolitis.

SELECTION CRITERIA
Randomised controlled trials (RCTs) and quasi-RCTs using nebulised hypertonic saline alone or in conjunction with bronchodilators as an active intervention and nebulised 0.9% saline as a comparator in infants up to 24 months of age with acute bronchiolitis.

MAIN RESULTS
We included 11 trials involving 1090 infants with mild to moderate acute viral bronchiolitis (500 inpatients, five trials; 65 outpatients, one trial; and 525 emergency department patients, four trials). All but one of the included trials were of high quality with a low risk of bias. A total of 560 patients received hypertonic saline (3% saline n = 503; 5% saline n = 57). Patients treated with nebulised 3% saline had a significantly shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline (MD -1.15 days, 95% confidence interval (CI) -1.49 to -0.82, P < 0.00001). The hypertonic saline group also had a significantly lower post-inhalation clinical score than the 0.9% saline group in the first three days of treatment (day 1: MD -0.88, 95% CI -1.36 to -0.39, P = 0.0004; day 2: MD -1.32, 95% CI -2.00 to -0.64, P = 0.001; day 3: MD -1.51, 95% CI -1.88 to -1.14, P < 0.00001). The effects of improving clinical score were observed in both outpatients and inpatients. Four emergency department-based trials did not show any significant short-term effects (30 to 120 minutes) of up to three doses of nebulised 3% saline in improving clinical score and oxygen saturation. No significant adverse events related to hypertonic saline inhalation were reported.

AUTHORS’ CONCLUSIONS
Current evidence suggests nebulised 3% saline may significantly reduce the length of hospital stay among infants hospitalised with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.
Nebulised hypertonic saline (3%) among children with mild to moderately severe bronchiolitis — a double blind randomized controlled trial

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BACKGROUND
To Assess the efficacy of nebulised hypertonic saline (HS) (3 %) among children with mild to moderately severe bronchiolitis.

METHODS
Infants aged 6 weeks to 24 months, with a first episode of wheezing and Clinical Severity scores (Arch Dis Child 67:289-93, 1992) between 1 and 8, were enrolled over 4 months duration. Those with severe disease, co-morbidities, prior wheezing, recent bronchodilator and steroid use were excluded. Patients were randomized in a double-blind fashion, to receive two doses of nebulized 3% HS (Group 1) or 0.9% normal saline (Group 2) with 1.5 mg of L-Epineprine, delivered 30 min apart. Parents were contacted at 24 h and 7 days. The principal outcome measure was the mean change in clinical severity score at the end of 2 h of observation.

RESULTS
A total of 100 infants (mean age 9.6 months, range 2-23 months; 61 % males) were enrolled. Patients in both groups had mild to moderately severe disease at presentation. On an intention-to-treat basis, the infants in the HS group had a significant reduction (3.57±1.41) in the mean clinical severity score compared to those in the NS group (2.26±1.15); [p < 0.001; CI: 0.78-1.82]. More children in the HS group (n = 35/50; 70.0 %) were eligible for ER/OPD discharge at the end of 2 h than those in the NS group (n = 15/50; 30 %; p < 0.001), and less likely to need a hospital re-visit (n = 5/50; 10.0 %) in the next 24 h as compared to the NS group (n = 15/50, 30.0 %; p < 0.001). The treatment was well tolerated, with no adverse effects.

CONCLUSIONS
Nebulized 3% HS is effective, safe and superior to normal saline for outpatient management of infants with mild to moderately severe viral bronchiolitis in improving Clinical Severity Scores, facilitating early Out-Patient Department discharge and preventing hospital re-visits and admissions in the 24 h of presentation.
INDICATIONS:

- Daily nasal hygiene;
- Moisturizing of nasal mucosa in case of dry air;
- Cleaning the nasal mucosa of dust, allergens;
- Prevention of infectious respiratory diseases;
- Comprehensive mucolytic treatment of bronchitis, bronchiolitis, cystic fibrosis, bronchiectasis;
- Comprehensive treatment of acute and chronic diseases of nasopharynx, nasal cavity and sinuses, adenoids hypertrophy in children, year-round and seasonal allergic rhinitis;
- Postoperative period after operations on the organs of the nasal cavity.

METHOD OF APPLICATION:

LORDE is assigned for inhalation use by inhalation through the mouth or nose via a nebulizer and for intranasal administration.

For inhalation: using 2-4 ml 2 times a day. If necessary, the multiplicity of administration can be increased.

Inhalation aerosol can be carried out using special face mask, mouthpiece or nasal cannula.