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Original article

Short-term effects on tolerability of inhaled hypertonic saline solution and hypertonic saline plus hyaluronic acid in cystic fibrosis patients

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Abstract. *Introduction* Inhaled Hypertonic saline (HS) solution has been proposed as a new therapy to increase the hydration of the airway surface in patients with CF. Some adverse events such as coughing, narrowing of the airways and salty taste could be modified by the combination of the solution with Hyaluronic acid. *Materials and methods* 30 children with cystic fibrosis received inhaled HS and inhaled HSHA for two consecutive days. The measurement of predicted FEV1% was performed before the treatment and 30 minutes post inhalation. *Outcome* The primary outcome was the evaluation of Forced Expiratory volume at first second (FEV1) % of predicted values measured before and after drug exposure (inhalation to HTS and HSHA respectively). *Conclusions* The administration of HS and HSHA showed a comparable safety profile. (www.actabiomedica.it)

Key words: cystic fibrosis, hyaluronic acid, hypertonic saline, tolerability, pulmonary function test, airway clearance techniques

Introduction

The role of chloride and sodium ion transport in the pathogenesis of chronic airway infection, inflammation, and bronchiectasis in Cystic Fibrosis (CF) has advanced substantially in recent years (1).

As a consequence of CFTR dysfunction (2), unrestrained sodium ion absorption and failure of active chloride ion secretion lead to decreased airway surface liquid volume and subsequent abnormal mucociliary clearance. Mucus retention predisposes the patient to chronic bacterial infection and inflammation, leading to lung damage and ultimately respiratory failure.

Hypertonic saline (HS) inhalation has been recently proposed as a new therapy to increase the hydration of the airway surface in patients with CF (3). HS expands airway surface liquid (4), thereby promoting a sustained acceleration of mucus clearance. It has been suggested that hypertonic saline is not a mucolytic because mucolysis is not its primary mode of action. However, hypertonic saline is capable of disrupting ionic bonds within the mucus gel, which could reduce crosslinking and entanglements. The Cystic Fibrosis Foundation guidelines support the use of inhaled HS as routine therapy because of its efficacy in improving lung function and reducing the number of pulmonary exacerbations (5).

Although the treatment is well tolerated by the majority of patients, some adverse events such as coughing, narrowing of the airways and salty taste are often reported, despite pre-treatment with an inhaled bronchodilator. These side effects make HS intolerable in about 8% of patients, and probably reduce adherence in those prescribed regular inhalations. Hyaluronic acid (HA) is a naturally occurring polysaccharide containing a repeated series of disaccharide units of glucuronic

acid and N-acetyl-glucosamine, occurring in many tissues and body fluids of vertebrates (6). It has several physiological functions: it has a barrier effect and regulates water homeostasis, prevents elastin injury by elastases, and modulates neutrophil elastase secretion (7). There is therefore evidence that HA may exert a protective effect against direct lung injury. Based on these observations, Buonpensiero et al. (8) tested the hypothesis that the combination of inhaled HS with HA could improve the pleasantness of HS, which would have the potential to increase the use and therefore, the benefit obtained from this treatment. The aim of the present study was to compare the pulmonary function test (PFT) after the inhalation of HS and the Hypertonic solution plus Hyaluronic acid (HSHA) to verify possible detrimental effects on FEV1%.

Material and methods

Study subjects

Participants were recruited from a regional pediatric CF center that is responsible for 190 patients < 18 years old. Thirty patients attending the clinic during the recruitment period were consecutively approached and informed about the study. Inclusion criteria for the evaluation were: an established diagnosis of CF, an age of at least 6 years, a forced expiratory volume in one second (FEV_1) of 50 percent or more of the predicted value, and clinically stable lung disease. CF diagnosis was confirmed by sweat testing (chloride ≥ 60 mmol/l by quantitative pilocarpine iontophoresis) and identification of two well-characterized genetic CFTR mutations. Exclusion criteria were: evidence of reactive airways or a clinical diagnosis of asthma. The study design was an open crossover trial comparing a single treatment of HS on one day and a single treatment of HS with HA on another day. The primary outcomes were the measure of pre-post difference of FEV1% evaluated after drug exposure (inhalation to HS and HSHA respectively) and baseline values.

At baseline, age, height and gender were recorded to allow the calculation of lung function values predicted by normative equations. Lung function testing was performed according to standardized criteria (American Thoracic Society/European Respiratory Society (2005) ATS/ERS Statement) (9) Current mucolytic therapy, pancreatic status, genetic analysis were recorded.

Lung function tests were performed with a laboratory function test equipment : Masterscope Viasys Health care.

Interventions

Salbutamol was administered at a dose of 200 μg 30 minutes before each inhalation of the study by metered dose inhalator. When participants were assigned to receive HS, they inhaled one 4 mL dose of 7% sodium chloride solution. When they were assigned to receive HS+HA, they inhaled one 4 mL dose of 7% sodium chloride solution with 0.1 % HA. This concentration of HA is the highest dose permitted for administration to humans in clinical research by the U.S. Food and Drug Administration and it is easily and comfortably inhaled. Delivery of both saline solutions was via a Pari LC plus nebuliser and a Pari Proneb Ultra compressor (Pari). During the study, all participants performed airway clearance physiotherapy using a positive expiratory pressure (PEP) mask, according to a standard treatment protocol. All the patients performed airway clearance physiotherapy with a time technique standardization.

Table 1. Characteristics of participants

Characteristic			Included participants (n=30)
Age (years), mean (range)			13.3 (6 - 18)
Gender n male (% male)			13 (43.3)
Height (m), mean (SD)			152.5 (±14.7)
BMI (kg/m^2), mean (SD)			19.35 (±2.54)
FEV_1 (%pred), mean (range)			86.7 (50 - 130)
Pancreatic insufficiency n (%)			27 (90)
Genotype	F508del/F508del	n %	12 (40)
	F508del/other	n %	12 (40)
	other/other	n %	6 (20)

BMI = body mass index, FEV_1 = forced expiratory volume in one second, kg = kilogram, m = meters, SD = standard deviation. %pred = % of predicted value for age, height and gender. Pancreatic insufficiency was determined by faecal elastase-1 below 100 μg/g feces

Table 2. Mean (SD), mean (SD) differences within, and mean (95% CI) differences between the Hypertonic Saline day and the Hypertonic Saline + Hyaluronic Acid day for FEV_1

	Pre HS n=30)	Post HS (n=30)	p (n=30)	Pre HTSHA (n=30)	Post HTSHA	p
FEV_1 (%pred) M ± DS	86.7±22.3	86.2±22	ns	89.5±23	91.3±24	ns

FEV_1 = forced expiratory volume in one second, HS = hypertonic saline, HTSHA = hypertonic saline + hyaluronic saline, %pred = % of predicted value for age, height and gender

Data analysis

Baseline lung function values were converted to percentages of the normal value predicted for the participant's age, gender and height. A paired t-test was used to compare the pre-post changes in FEV_1 in the two intervention-groups.

Results

Baseline characteristics were summarized in table 1. All 30 patients completed the study. No patients reported adverse events during the inhalation of both drugs. The median values of FEV1%, measured 30 minutes after the inhalation and at baseline, were not statistically different in the two intervention-groups. Data are shown in Table 2.

Discussion

As we have previously reported, the Cystic Fibrosis Foundation guidelines support the use of inhaled HS as a routine therapy (5) because of its efficacy in improving lung function and reducing the number of pulmonary exacerbations. These guidelines have led to an increase of the use of HA as standard therapy over the last decade. A proportion of 8% of patients could not benefit from this treatment because of its pleasantness and side effects. The addition of HA to HS could improve pleasantness and consequently adherence to the therapy. Our data showed that no significant decrease in pulmonary function test occurred after the inhalation of HSHA. These data can be considered as a safety data profile of HSHA inhalation in stable cystic fibrosis patients.

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