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The Acute Effect of Inhaled NaCl 5%, Per CF TRUST Protocol, on Spirometry Indices in Patients Over Six Years with Cystic Fibrosis

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Abstract

Background: Our aim was to investigate the acute effect of inhaled NaCl 5% on spirometry indices in patients aged over six years with cystic fibrosis (CF).
Methods: 44 children over 6 years of age with CF took part in this study. Spirometry indices were measured. After receiving two puffs of salbutamol spray, the children were administered with 5 ml NaCl 5% by a medical compressed air system using a nebulizer kit and immediately a spirometric test was taken again. Spirometry results were recorded and the data were analyzed by SPSS v.18.
Results: The percentages of the annual decline of forced expiratory volume in one second (FEV_1) were 10.12 ± 31.28, 7.26 ± 17.10, and 13.8 ± 21.7 in children aged 6 - 8 years, 9 - 12 years, and over 13 years, respectively. There were significant differences in FVC, FEV_1/FVC, MEF_{50}, MEF_{75}, $MMEF_{25/27}$ before and after hypertonic NaCl 5% inhalation ($P < 0.05$). A significant decline in FEV_1 was observed only in 2% of the children.
Conclusions: Patients with CF exhibited a suitable response to acute inhalation of hypertonic NaCl 5%.

Keywords: Cystic Fibrosis, Hypertonic Saline Solution, Spirometry

1. Background

Cystic fibrosis (CF) is one of the most common and life-threatening genetic diseases (1) and a type of recessive autosomal disorder in ion carriers of epithelial cells because certain mutations occur in the CF transmembrane conductance regulator (CFTR), most frequently at position 508 (ΔF508) (2, 3). In addition to exerting certain effects on cAMP-dependent chloride channels and reducing the release of epithelial chloride ion, CFTR dysfunction causes an increase in the absorption of epithelial sodium channel-mediated ion in the airway superficial epithelium (4). These disorders can lead to the formation of an adhesive and thick mucus that causes lung obstruction, respiratory infections, digestive problems (1), inflammation and degeneration and ultimately, respiratory failure (5).

Treatment for CF is therefore based on the clearance of the airway using various methods such as physical therapy and vibration, mechanical methods, breathing techniques, body position, and hypertonic saline (6). The second-line treatment is to limit bacterial and infectious colonization using oral, venous, and inhaled antibiotics (4). Moreover, increased airway surface liquid causes improvement of mucus clearance in patients with CF (7). Inhaled hypertonic saline is used to moisturize the airway in people over six years of age, and according to more recent investigations, in infants and children (7), and as a mucolytic agent before and during airway clearance (8, 9). This substance improves pulmonary function and respiratory symptoms and causes a decrease in respiratory attacks and an increase in the intervals between the attacks (5, 10, 11). However, hypersaline is not tolerated by some patients (12) and it should be further investigated for use (5, 13). To study pulmonary function in patients with CF, spirometry and associated indices are measured. However, forced expiratory volume in one second (FEV_1) is an important spirometry index to investigate pulmonary functions in these patients because it can help determine the types and severity of the involvement (14). Moreover, spirometry indices should be investigated to examine the course of pulmonary function after hypertonic saline administration (10).

It is highly necessary to seek out new therapies to enhance the quality of life and life expectancy among children with CF (13). In addition, with regards to the problems caused by this disease in the patients, this study was con-

ducted to investigate the acute effect of nebulized NaCl 5% on spirometry indices and pulmonary function in CF patients over 6 years referring to the clinic of lung disease in Mofid Children hospital.

2. Methods

In this clinical trial, the pulmonary function of all children over 6 years old with CF referring to the clinic of lung disease in Mofid Children hospital, Tehran, was investigated in 2014 - 2015. Participants were selected by convenience sampling. In this study, all patients referring to the clinic during one year were studied. The inclusion criteria were having phenotypic characteristics of CF and positive sweat chloride test and being over 6 years old, and the exclusion criteria were the inability to undergo spirometry test, severe reaction to hypersaline 5%, and not volunteering to participate in the study.

First, all eligible children, according to the clinical symptoms or acquisition of CF in one of the family members alongside two turns of positive sweat chloride test (above 60 mM/L), were assessed during a six-month period. The data were gathered by examination, observation, and interview. The instrument of data collection consisted of two sections. The first section was to gather demographic data such as age, gender, patient's main complaint, physical indices, and a history of infection with Pseudonomas aeruginosa. The second section contained items about spirometry findings.

At baseline, the first spirometry test was conducted on the patients using Master Scope-PC (Jaeger, Germany). According to the protocol of CF, 30 minutes after receiving two puffs of inhaled salbutamol through Valve Holding Chamber (AsanNafas, Medical Technology, Tehran, Iran), 5 mL NaCl 5% was administered by a medical compressed air system using a nebulizer kit (Hite Care Nebulizer, Hitec Medical, China) continuously within 10 minutes, and immediately the second spirometry test was conducted using the same instrument. Spirometry results were recorded in a special form. The study protocol was approved by ethics committee of Shahid Beheshti University of Medical Sciences (no.: IR.SBMU.RETECH.REC.1396.49). Data analysis was conducted by SPSSv18. t test, Crosstabs, and ANOVA were used to compare the data on pulmonary function in the previous year, before the intervention (vaporized Na 5%) and after the intervention. Confidence interval (CI) was considered 95%.

3. Results

Seventeen (38.6%) children were female and 27 were male. The mean age of the children was 11.05 $\pm$ 6.01 years. Regarding age range, 22 (50%) children were 6-8 years, 9 (20.5%) were 9 - 12 years, and 13 (29.5%) were 13 years or over. The mean age at diagnosis was 2.22 $\pm$ 3.91 years. The mean weight of the children was 34.37 $\pm$ 17.60 kg, the mean height was 137.92 $\pm$ 22.38 cm, and the mean BMI was 16.95 $\pm$ 4.12. The mean number of breaths per minute was 25.48 $\pm$ 8.54. Twenty (45.5%) patients were positive for *P. aeruginosa* colonization. The most common CF-related complaint at baseline was steatorrhea (54.8%).

Mean FEV_1% before hypertonic NaCl 5% inhalation and the annual decline of FEV_1% in different age groups are shown in Table 1.

Table 1. Comparison of Mean FEV_1% Before Hypertonic NaCl 5% Inhalation and Annual decline of FEV_1% in Different Age Groups in Children with Cystic Fibrosis

	Time	
Age group	**% Before Intervention**	**Annual Decline of FEV_1%**
6 - 8 year	80.74 $\pm$ 27.58	10.12 $\pm$ 31.28
9 - 12 year	84.28 $\pm$ 18.79	7.26 $\pm$ 17.25
13 $\geq$	76.76 $\pm$ 27.21	13.18 $\pm$ 21.27
P Value	0.796	0.875

According to the ANOVA test, the annual decline of FEV_1% was not significantly different between boys and girls (P = 0.16). *P. aeruginosa* colonization with and without an annual decline of FEV_1% was seen in eight (88.9%) and six (54.6%) children, respectively. Spearman correlation coefficient showed that there was no statistically significant association between *P. aeruginosa* colonization and the annual decline of FEV_1% in the children (P = 0.104).

The findings on the effect of hypertonic NaCl 5% inhalation on spirometry indices are summarized in Table 2. The results of the paired t-test indicated that there were significant differences in forced vital capacity (FVC), FEV_1/FVC, maximum expiratory flow rate at 50% of vital capacity (MEF_{50}), maximum expiratory flow rate at 75% of vital capacity (MEF_{75}), and maximum mid-expiratory flow ($MMEF_{25/27}$) between before and after hypertonic NaCl 5% inhalation (Table 2).

After hypertonic NaCl 5% inhalation according to the protocol, 38 (90.5%) children exhibited no decline in FEV_1, three had (7%) 5% -10% decline in FEV_1, and one had over 10% decline in FEV_1.

4. Discussion

The present study was conducted to investigate the acute effect of nebulized NaCl 5% on spirometry indices in patients over six years with CF. The main CF-related complaints leading to diagnosis were steatorrhea and growth

Table 2. Distribution of Spirometry Indices Before and After Hypertonic NaCl 5% Inhalation in Children with Cystic Fibrosis[a]

Index	Before Intervention	After Intervention	Level of Significance
FEV_1	80.29 ± 25.52	82.35 ± 29.25	0.430
FVC	77.64 ± 22.04	82.13 ± 22.81	0.006
FEV_1/FVC	87.88 ± 9.99	85.85 ± 10.75	0.020
MEF_{25}	76.04 ± 52.52	108.10 ± 207.84	0.291
MEF_{50}	77.09 ± 36.12	87.42 ± 42.30	0.003
MEF_{75}	84.71 ± 34.16	91.81 ± 32.59	0.023
$MMEF_{25/75}$	76.84 ± 37.58	83.91 ± 42.04	0.036

[a]Values are expressed mean ± SD.

disorders. The cause of steatorrhea in CF patients is pancreatic exocrine insufficiency that in turn is due to the closure of ampulla of Vater. This issue is associated with the limited effect of pancreatic enzymes such as lipase (15, 16) and therefore, certain symptoms such as malabsorption of nutrients and excessive and bulky diarrhea, alongside steatorrhea, are the gastrointestinal outcomes of CF (12).

In the present study, after the intervention, most indices including FVC, FEV_1/FVC, MEF, and $MMEF_{25/75}$ showed increasing trends. This finding shows that the patients exhibited a suitable response to acutely nebulized hypersaline 5%. Elkins et al. investigated long-term (48-week) inhaled hypertonic saline in patients with CF. The findings demonstrated that the group administered with hypersaline 7% had higher FVC and FEV_1%, but no significant difference was seen in FEF_{25-75} in this group. However, the use of hypersaline was recognized as a safe, inexpensive, and efficient method to treat respiratory problems in patients with CF (11). A study reported that certain indices such as FEF, FEV_1, and quality of life improved significantly after administration of inhaled hypersaline (17).

A study demonstrated that the infants and children with CF exhibited acceptable tolerance and adherence to hypersaline 7% in short-term (18). Because hypersaline has various functions, it may be difficult to classify hypersaline into a specific class of drugs. However, hypersaline nebulizer administration can have mucolytic, expectorant, mucokinetic, ion-transport modifying, and other mucoregulatory properties (10).

Inhaled hypertonic saline improves water absorption on airway surface via an osmotic process and causes the clearance of mucus and improvement of pulmonary function; therefore, rehydration therapies prevent progression of infection and decline of pulmonary function in early years of life (4). Despite hypersaline's effects on reducing CF complications, a respiratory bronchodilator is necessary to reduce the complications and increase tolerance in the patients (19), because the administration of hypersaline alone can cause narrowing of the airway and certain complications such as a cough, wheezing, and chest tightness (10).

In the present study, after hypertonic NaCl 5% inhalation, approximately 90% of the patients were found to have no decline in FEV_1 percentage. In some studies, pulmonary exacerbation was lower in patients treated with hypersaline, the patients were satisfied with this treatment, and the treatment was described efficient (4, 8, 10).

A remarkable finding in this study was that the percentage of the annual decline of FEV_1 was 10.12 ± 31.28, 7.26 ± 17.10, and 13.8 ± 21.7 in children aged 6 - 8 years, 9 - 12 years, and over 13 years, respectively. This variable in Konstan's study was reported 1.12% in 6 to 8-year-old children, 2.39% in 9 to 12-year-old ones, and 2.34% in those over 13 years of age. This finding represents a considerable annual decline of FEV_1 in patients with CF in Iran. Therefore, new therapeutic strategies and policies should be adopted to maintain pulmonary function and life expectancy among these patients.

In the present study, 18 patients were positive for *P. aeruginosa* colonization, and *P. aeruginosa* colonization was not significantly associated with the annual decline of FEV_1. Elkins et al. study demonstrated that hypersaline administration was not associated with predisposition to inflammation and infection in patients with CF (11). Dehydration of epithelial cells mucosa and dysfunction of mucociliary clearance in the airway due to a defect in chloride canals may lead to the stability of mucus in the airway, which predisposes patients with CF to chronic infection (18, 19). Hypersaline leads water toward the surface of the epithelial cells through osmosis and increases dilution of mucus. As a result, an unsuitable environment for microbial growth is created and the inflammation severity reduces (20).

Nebulised ß2-agonists are the most common agents prescribed for CF patients but studies that have confirmed their benefit are not adequately reliable (21). The dose and administration of ß-adrenergic agonists continue to widely vary even 24 years after publishing Stainfoth et al.'s study (22). The British thoracic society (BTS) guidelines for nebulizer therapy emphasize the lack of studies with CF patients. Physicians consider bronchodilator administration a good practice but the evidence on efficacy or optimal dosage is scant. No profound change has occurred since the publication of these guidelines. In 2005, the Cochrane Collaboration declared that 'despite the wide-scale and often long-term use of bronchodilators in CF, there is little objective evidence regarding their efficacy (23). In a study at the Leeds Adult CF Unit in 2006, 15 (total number: 83,

18.1%) patients showed significant responses to reversibility testing with nebulized salbutamol in annual assessment. The main predictor of a positive response was lower pre-existing lung function. No trial has yet been conducted to study the effect of terbutaline or fenoterol in comparison with placebo in the population with CF (24).

4.1. Conclusions

The acute effect of nebulized hypertonic NaCl 5% helped improve certain indices such as FVC, FEV_1/FVC, MEF_{50}, MEF_{75}, and $MMEF_{25/27}$. Although most patients exhibited suitable responses to inhaled hypertonic NaCl 5%, the incidence of unexpected complications particularly at the beginning of the treatment with NaCl 5% in a small proportion of the patients should be rigorously studied. A limitation of the present study was the lack of conducting pulse oximetry before and after the intervention.

It is recommended to study different concentrations of hypersaline at different intervals as well as simultaneous administration of antibiotics and NSAIDs in future studies.

Footnote

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