ORIGINAL ARTICLE

LONG-TERM USE OF INHALED HYPERTONIC SALINE IN CHILDREN AND ADOLESCENTS WITH CYSTIC FIBROSIS: EXPERIENCE FROM A TERTIARY CARE CENTER IN A LOW AND MIDDLE INCOME COUNTRY

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Background Long term hypertonic saline use has been found to improve mucus transport, airway hydration, and mucociliary clearance in patients with cystic fibrosis. However, the effect of hypertonic saline on the outcomes of patients with cystic fibrosis is not well established. The aim of our study was to determine the long-term use of hypertonic saline in reducing pulmonary exacerbations, length of hospital stay and pseudomonas colonization in patients with cystic fibrosis admitted for treatment at a tertiary care referral center. **Methods:** Retrospective cohort study was conducted on 71 patients with cystic fibrosis. Patients ranged in age between 3–18 years. All patients with two to five pulmonary exacerbations in the preceding six months were included in the study. Those who received regular inhaled 3–7% hypertonic saline twice daily during their admission and till 6 months after discharge from hospital were categorized as hypertonic saline (HTS) group. Patients who did not receive regular hypertonic saline for 6 months were included in the non-hypertonic saline (NHTS) group. Data was analyzed at the end of one year. **Results:** The HTS group had 37 patients whereas, the NHTS group had 34 patients. Mean number of exacerbation episodes was significantly lower in HTS group (2.18±0.84) as compared to NHTS group (3.67±0.91) (p<0.01) whereas, length of hospital stays and frequency of pseudomonas colonization did not significantly differ between the two groups (p=0.78 and p=0.12 respectively). The mean number of pulmonary exacerbations also significantly reduced from 3.11±1.07 to 2.18±0.84 p-value <0.01 in the HTS group over the follow-up period of one year. **Conclusion:** Long term hypertonic saline therapy is beneficial in patients with cystic fibrosis in preventing pulmonary exacerbations and subsequently reducing morbidity**.**

Keywords: Hypertonic Saline; Pulmonary Exacerbation; Pseudomonas colonization

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INTRODUCTION

Cystic fibrosis (CF) is a hereditary disease with multi-organ manifestations due to the absence of a functional cystic fibrosis transmembrane conductance regulator (CFTR) protein, resulting in abnormal membrane electrolyte transport. The 'isotonic volume depletion hypothesis', explains the abnormalities in CF caused by a combination of abnormal hyper-viscous secretions, impaired mucociliary clearance and bacterial overgrowth which alter the airway and further weaken host defenses.[1] *Pseudomonas aeruginosa* is found to be the most commonly involved organism in the airways of CF patients during acute exacerbations.[2,3]

Cystic fibrosis is the most common cause of early mortality in the Caucasian population globally among the autosomal recessive disorders.[3] The prevalence of CF in Pakistan is difficult to ascertain and the disease goes mostly underdiagnosed due to limited availability of diagnostic tools, registries, and neonatal screening programs.[4,5]

Previous studies have shown that majority of the hospitalizations in CF patients are due to pulmonary exacerbations.[6,7] Each exacerbation episode carries a risk of permanent loss of lung function, and it is estimated that in around 25% of the episodes, patients are unable to regain 90% of their previous baseline forced expiratory volume (FEV_1).

Therefore, the frequency of respiratory exacerbations is closely related to chronic reduction in lung function. There is a need to develop pre-emptive strategies to avoid frequent exacerbations. Clinical trials mostly from developed countries have shown interventional strategies like inhaled antibiotics, dornase alfa and CFTR modulators to be effective in altering the disease course. However, access to these is limited due to lack of resources and social constraints. There are differences in CF care and outcomes between developing and developed

countries in terms of life expectancy, quality of life, nutrition, and lung function.[8]

Inhalation of hypertonic saline has improved lung function and reduced exacerbation rates in patients with CF.[9] Hypertonic saline is inexpensive, safe, and well tolerated in young children and it has become an acceptable mucolytic agent for CF patients.[10] Therefore, the aim of our study is to determine the use of long-term inhaled hypertonic saline in reducing pulmonary exacerbations, length of stay and *Pseudomonas* colonization.

MATERIAL AND METHODS

We conducted a retrospective cohort study from January 2014 to December 2018. The study was conducted at the Aga Khan University Hospital, Karachi, Pakistan. Our eligibility criteria was as follows; cystic fibrosis patients aged 3 years to 18 years who presented with 2–5 pulmonary exacerbations in previous six months were included in the study and assigned to either of the two groups based on their hypertonic saline use. Patients who were started on regular HTS but did not continue for the total duration of six months and those patients whose compliance was questionable were excluded from the study. Similarly, patients who were lost to follow up or had missing data were also excluded from our study. Patients with associated allergic bronchopulmonary aspergillosis (ABPA) were excluded from the study.

Cystic fibrosis Patients who were started on regular hypertonic saline twice daily and continued to use HTS for six months were categorized as hypertonic saline (HTS) group. Patients who were not started or not on regular hypertonic saline for 6 months were categorized as non-hypertonic saline (NHTS) group. These patients were then followed up for one year to assess outcomes in terms of 1) number of exacerbations per year, 2) average length of stay per exacerbations and 3) Pseudomonas colonization. (Figure-1)

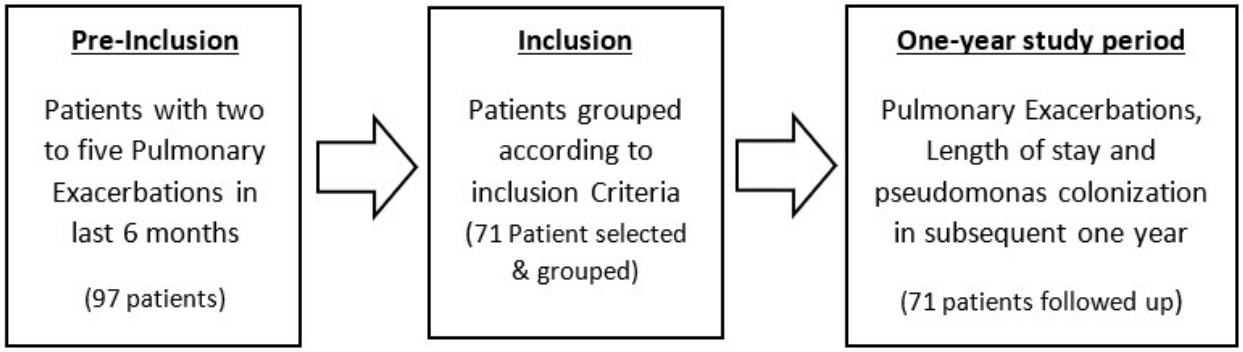

Figure-1: Study Design

Online pharmacy data and individual patients' chart were reviewed to ensure compliance in labelling patients into groups. CF pulmonary exacerbations is defined as patients who were admitted in the hospital or started on intravenous antibiotics and presented with respiratory distress, increased frequency of cough, increased sputum production, increase work of breathing, and/or having new crackles on auscultation or new radiological finding on chest x-rays as new consolidations ± collapse or infiltrates.[11,12]Tracheal swab or sputum cultures were documented for the growth of organism during study period. Ethical approval was taken from Ethical Review Committee of the hospital. Data was collected from patient's charts, online admission data and online -pharmacy registry.

Independent variables included age and gender, height and weight on admission, duration of hospitalization, sputum culture results and HTS use during subsequent hospitalizations in the following year were documented. Dependent variable was pulmonary exercabations.

Data was analyzed using SPSS version 22. Continuous variables were reported as mean and standard deviation, while categorical variables were reported as frequency and percentages. The Independent sample t-test was used to assess significant difference between HST and non-HST groups. The paired student *t*-test was used to assess significant difference between pre- and post-hypertonic saline exposure with in the same groups. *p*-value of ≤ 0.05 was considered significant.

Chi-Square test was used for qualitative variables including intermittent use of Azithromycin and frequency of pseudomonas colonization.

RESULTS

Out of 97 patients, 71 patients were selected as per inclusion criteria and followed for one year. During study period, 37 patients received regular hypertonic

saline nebulization and were included in the HTS group, the remaining 34 patients were included in the non-HTS group. Baseline characteristics of both the groups are described in table-1.

The mean number of exacerbation episodes were significantly lower in the HTS group (2.18±0.84) as compared to the non-HTS group (3.67±0.91) at one-year after the start of treatment (*p*-value <0.01). There was no significant difference in the length of stay and *pseudomonas* colonization between both the groups. (Table-2)

The mean number of pulmonary exacerbations also significantly reduced from 3.11±1.07 to 2.18±0.84 *p*-value <0.01 with in same HTS group over the follow-up period of one year. This was not the case in the non-HTS group, where the mean number of pulmonary exacerbations increased from 3.20±1.11 to 3.67±0.91, *p*-value =0.04 (Table-3) There was no significant difference in the length of stay both pre and post HTS use.

Table-1: Demographic details and clinical characteristics of patients in two groups

	HTS group (n=37)	Non-HTS group (n=34)	*p*-value
Gender (M:F)	1.5: 1	1.3: 1	
Mean age (years), mean ± SD	8.85±7.15	9.26±8.34	0.69
Mean age at diagnosis (Years) mean ± SD	3.45±2.78	3.97±2.59	0.23
Mean Weight (kg) mean ± SD	19.54±4.36	17.91±3.5.3	0.86
Mean height (cm) mean ± SD	145.35±7.39	137.74±8.75	0.91
Mean Pulmonary Exacerbation Pre-Induction period mean ± SD	3.11±1.07	3.20±1.11	0.74
Regular use of intermittent azithromycin (n)	14 (37.83%)	16 (47.05%)	0.98
Mean length of stay Pre-induction period (days) mean ± SD	4.62±0.98	4.82±1.02	0.40
Pre induction Pseudomonas Colonization (n)	18 (48.64%)	15 (44.11%)	0.81

Table-2: Difference between the groups at one year follow up

	HTS group (n=37)	Non-HTS group (n=34)	*p*-value
Mean Pulmonary Exacerbation mean ± SD	2.18±0.84	3.67±0.91	<0.01
Pseudomonas Colonization (n)	19 (51.35%)	16 (47.05%)	0.78
Mean Length of stay (days), mean ± SD	4.48±0.69	4.85±1.20	0.12

Table-3: Pre and Post recruitment pulmonary exacerbations and length of stay

	Recruitment	one year follow-up	*p*-value
HTS group			
Mean Pulmonary Exacerbation, mean ± SD	3.11±1.07	2.18±0.84	<0.01
Mean length of stay(days), mean ± SD	4.62±0.98	4.48±0.69	0.44
Non-HST group			
Mean Pulmonary Exacerbation, mean ± SD	3.20±1.11	3.67±0.91	0.04
Mean length of stay(days), mean ± SD	4.82±1.02	4.85±1.20	0.87

DISCUSSION

We observed that regular treatment with 3–7% hypertonic saline for six months had a significant impact on the mean number of pulmonary exacerbations in CF patients as compared to standard treatment at one year of follow up. However, it does not affect length of hospital stay and *pseudomonas* colonization.

Various trials have been conducted to study the efficacy of long term hypertonic saline use in CF patients with most studies being conducted in adults with limited data available for infants and children.[13] In children, as opposed to adults, the progression of lung disease is not well established and the early initiation of long-term HTS use can have positive effects on prevention of disease progression. Moreover, long term use has been seen to be tolerable with fewer side effects in previous studies, but this could not be explored in our study.[14] A number of theories attempt to explain how hypertonic saline aids in slowing the progression of lung disease in CF patients, one of the possible ways by which it works is by inducing an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid to improving the rheology of mucus. It also breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and lowering the viscosity and elasticity of the mucus secretion, it is also known to stimulate cilial beat via the release of prostaglandin E2.[14–16]

The results of our study concur with previously published studies which compared twice daily administration of hypertonic saline over a period of 48 weeks with isotonic saline. It was also reported that hypertonic saline group had a lower rate of exacerbations and improved overall quality of life.[13] Another study conducted in all age groups found HTS to be effective in lowering exacerbations

in all stages of CF lung disease severity.[17] However, a randomized control trial study conducted in 321 preschool children with CF (between the ages of 4–60 months) compared hypertonic saline versus isotonic saline and did not identify any significant difference in respiratory exacerbations.[18] A trial conducted in Germany studied 42 infants less than 4 months of age with CF and found that use of hypertonic saline improved the lung clearance index and resulted in overall weight gain but rate of exacerbation episodes did not differ between the hypertonic saline and isotonic saline groups.[19]

Even though our study found no significant difference between the two groups in terms of length of hospital stay, several trials have evaluated the effects of HTS on length of stay as a primary outcome, these findings were summarized in a meta-analysis which found the length of hospital stay to be 0.41 days shorter in case of patients receiving hypertonic saline.[20] Given the hypothesis that hypertonic saline could inactivate endogenous antimicrobial compounds in patients with cystic fibrosis.[21,22] Our study could not find any convincing evidence in support for the above due to clinical nature of the research and retrospective design.

To the best of our knowledge this is the first study of its kind performed to assess the role of hypertonic saline in children and adolescents in Pakistan. It will facilitate the development of standardized local guidelines to achieve better outcomes and maximize survival benefit. Additionally, this adds to the pool of knowledge especially from a developing country where the resources are limited. Further studies from our region are needed for greater understanding of the natural history of the disease in this part of the world.

The limitations of our study are principally its retrospective nature and lack of randomization, unavailability of detailed pulmonary function tests and side effect profiles; moreover, there was no uniform protocol in place to assess compliance with therapy. Prospective randomized controlled studies with larger numbers of included participants are warranted to better assess the benefit of inhaled HS at varying stages of CF lung-disease severity in our settings.

CONCLUSION

Use of inhaled hypertonic saline during hospitalization for acute exacerbation of CF was associated with a lower rate of pulmonary exacerbation with respect to standard treatment. There was, however, no difference in length of hospital stays and *pseudomonas* colonization amongst HTS and NHTS groups.

Conflict of interest: None

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AUTHORS' CONTRIBUTION

DA, SS and FM helped in conception and design of the study, SS and NA did analysis and interpretation of data; AA, NA and DA contributed in drafting the work and revising it critically for important intellectual content. All authors approved the Final version for publication and agreed to be accountable for all aspects of the work.

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