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The Effect of Outpatient Management of Cystic Fibrosis Exacerbation on Pulmonary Function Tests: A Clinical Trial

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Abstract

Background: Cystic fibrosis (CF) is an inherited disease which involves multiple organs including respiratory tract. It results in chronic respiratory signs and symptoms which exacerbate with frequent lung infections. The majority of exacerbations require hospitalization and intravenous antibiotic therapy as part of the management. The aim of this survey was to study the effectiveness of outpatient management of pulmonary exacerbations on pulmonary function tests.

Methods: This randomized clinical trial included all CF patients older than 6 years old who presented with a pulmonary exacerbation and were able to perform Spirometric tests. All eligible CF patients first referred to pulmonary function tests center to determine forced expiratory volume in the first second (FEV1), residual volume (RV), total lung capacity (TLC) and airway specific resistance (SRaw). Then, they were treated outpatiently for 2 to 4 weeks and after that, they underwent all the tests again; and the participants' improvements in pulmonary function tests after outpatient treatment were investigated.

Result: In this study, 32 patients were enrolled including 13 women (40.6%) and 19 men (59.4%). Mean and standard deviation (SD) of pulmonary variable, before and after the treatment were investigated. All of them were statistically significant. Sub-analysis of data based on gender was also performed showing that outpatient treatment led to significant improvements in all of the variables except for the percentage of RV in females (p value = 0.08).

Conclusion: The findings revealed that outpatient management of CF exacerbations effectively improved values of FEV1, SRaw and TLC along with reducing RV values and air trapping. Thus, applying this method on appropriately selected CF patients, may prevent unnecessary hospitalization and subsequent disadvantages.

Key Words: Cystic fibrosis, Exacerbation, Outpatient, Pulmonary function test.

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1- INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive inherited disease which involves multiple organs including respiratory tract, intestinal and biliary tracts, pancreas, GU tract, and sweet glands (1). CF is typically a pediatric disease. The age of onset of symptoms in most of the patients is the first five years of life (2, 3). The disease is a result of CFTR gene mutation which coded CFTR protein, the one that plays the role of a chloride channel and is expressed in large amounts in the mentioned organs (1, 4). The clinical significance of this mutation in the respiratory tract is increased viscosity and thick, sticky and mucosal secretions in airways (5), which explain in part the patient's complaint of coughing or wheezing, etc. This chronic course exacerbates with frequent lung infections over time which in turn results in progressive respiratory dysfunction, respiratory failure and ultimately death (1, 6). Indeed, Pulmonary Exacerbations (PEx) play an important role in long term morbidity and mortality (7).

To minimize these awful complications and improve the quality of life and survival of affected patients, continued clinical care along with accurate and adequate management of PEx is needed.

On the other hand, as other chronic diseases, the high costs of routine cares, medications and equipment highly charge CF patients over time; in addition, hospitalization in children results in school absence and psychological burden. We can conclude that despite intravenous antibiotic therapy in hospital settings, is the mainstay of treatment in PEx, outpatient management in some selected cases could be beneficial. In this study we evaluate the effectiveness of outpatient management of PEx by several measures, which lead to improved patient's life quality and decreased family expenses, compared to hospitalization.

2- METHODS

This study was a pretest-posttest interventional clinical trial conducted at Children's Medical Centre hospital (CMC), the hub of excellence in pediatrics in Iran, located in Tehran, Iran.

All the eligible patients initially referred to the CMC pulmonary tests center to determine their lung volumes and capacities including forced expiratory volume in the first second (FEV1), residual volume (RV) and total lung capacity (TLC) by spirometry and body box (plethysmograph) machines and their airway specific resistance (SRaw) by impulse oscillometry (LOS).

After that, the patients were outpatiently treated, according to the accepted therapeutic protocol of CF foundation of CMC (**Table 1**), for 2 to 4 weeks based on the severity of their signs and symptoms.

After complement of the treatment course, the patients underwent all the previous tests again.

2-1. Inclusion and Exclusion Criteria

Most of the patients referred to the center's CF foundation form April to December 2019, were enrolled in the study. Inclusion criteria were PEx phase in a proven CF patient older than 6 years old who was able to perform Spirometric tests. Exclusion criteria were any physical or mental disability that interferes with performing the tests, or any medical indication for intravenous (IV) treatment, including more severe attacks or ill condition of the child, etc.

2-2. Data analysis

We used central mean and standard deviation to describe the quantitative variables and for qualitative variables we implemented the frequency and percentages. Normal distribution of data was confirmed using Kolmogorov-Smirnov test. To compare the mean of

before and after pairs, paired t-test was used. All the information obtained from this study was entered into SPSS version 23 software and analyzed at a significance level of 5% (P-value < 0.05).

3- RESULTS

The participants were selected from CF patients older than 6 years who were in exacerbation phase and were physically and mentally able to perform pulmonary tests. Outpatient treatment was performed with antibiotics based on physician assessment and supportive cares.

In this study, 32 patients were enrolled including 13 women (40.6%) and 19 men (59.4%). The mean age of the patients was 12.6 ± 2.9, the minimum age was 6 and the maximum age was 17 years. **Table 2** shows means and standard deviations (SD) of the pulmonary variables, before and after the treatment in all the patients (values and percentage of values). All of them were statistically significant. **Table 3** shows sub-analysis of data based on gender which shows that the treatment significantly affects all of the variables (values and percentage) except for the percentage of RV in females (p-value = 0.08).

4- DISCUSSION

In the current research, we studied four spirometeric parameters before and after the outpatient treatment in 32 CF patients with PEx: FEV1, SRaw, RV and TLC.

We found that before the initiation of oral treatment, mean ±SD of FEV1 regardless of gender, was 64.16 ±29.84%, which is lower than normal, while after the treatment it improved to 69.58 ±32.03%; showing a statically significant improvement. Sub-analysis of data in female and male gender separately, also showed similar results. Based on several studies, FEV1 is a particularly important parameter. In a large-scale study conducted in Canada in 2015, Lukic and Coates explained that FEV1 is a valuable marker in CF patients for detecting disability; however, in mild and early stages of the disease it is not so sensitive. They, thus, suggest FEV1 to FVC ratio (8).

Table-1: The accepted outpatient treatment protocol for CF exacerbation in CMC

Airway clearance therapy	Nebulized Hypertonic saline, nebulized Ventolin, chest physiotherapy (at least 4 times a day)
Antibiotic therapy based on sputum culture results and antibiogram	Oral/I.V antibiotic therapy against existing micro-organisms found on sputum culture
Treatment of dehydrations	Dehydration treatment and electrolyte corrections by taking oral liquids

Table-2: Mean ± SD of pulmonary variables before and after the treatment

Pulmonary variables	Percentage of values			Values		
	Before Mean ± SD	After Mean ± SD	p-value	Before Mean ± SD	After Mean ± SD	p-value
SRaw	139.84±21.34	127.98±18.45	0.00	6.4±1.38	5.9±1.32	0.00
FEV1	64.16±29.84	69.58±32.03	0.00	1.66±0.94	2.66±4.92	0.02
RV	224.87±87.42	219.49±74.28	0.00	2.03±0.85	1.8±0.79	0.00
TLC	99.92±12.92	108.63±16.32	0.00	3.47±1.04	3.83±1.15	0.00

Table-3: Mean ± SD of pulmonary variables before and after the treatment based on gender

Variable			Pulmonary variables			
			SRaw	FEV1	RV	TLC
Percentage of values	Male	Before Mean ± SD	141.84±21.93	68.30±30.32	215.77±71.80	96.89±13.37
		After Mean ± SD	131.20±18.50	74.46±34.59	203.83±71.80	106.19±17.39
		P value	0.00	0.00	0.04	0.00
	Female	Before Mean ± SD	136.91±20.96	58.08±29.22	238.18±108.18	104.34±9.30
		Before Mean ± SD	123.28±18.04	62.44±27.62	242.39±74.60	112.20±14.55
		P value	0.00	0.00	0.08	0.02
Values	Male	Before Mean ± SD	6.27±1.53	1.82±1.07	1.84±0.62	3.43±1.09
		After Mean ± SD	5.79±1.44	2±1.20	1.6±0.62	3.76±1.14
		P value	0.00	0.00	0.00	0.00
	Female	Before Mean ± SD	6.66±1.14	1.41±0.68	2.31±1.07	3.52±1.02
		After Mean ± SD	6.19±1.14	3.66±7.66	2.09±0.94	3.93±1.21
		P value	0.00	0.02	0.00	0.00

Later in 2017 van Horck et al., in a multi-center study, asked 49 CF children to fulfill a respiratory symptom questionnaire along with home monitoring of FEV1 three times a week. The found that FEV1% pred (percentage of predicted) at the beginning of PEx was significantly lower in the intervention group as compared to the non-exacerbation groups. They concluded that a combination of these two measures is a sensitive and specific predictor of early stages of PEx in CF children (9).

In the current study, FEV1 values significantly improved after the oral antibiotic therapy, which emphasize the role of FEV1 in the follow-up treatment.

As showed in **Table 2**, mean ± SD of SRaw was initially 139.84 ±21.34% and after the treatment, they significantly improved to 127.98±18.45% (P-value: 0.00). Investigating this parameter, separately, in female and male genders led to the same results. Nielsen et al., in 2004, in a 4 years prospective study evaluated SRaw by several methods in CF patients. They concluded that the mean SRaw and FEV1 are always lower than normal ranges in CF patients and so they are advantageous (10). In 2012, Topalovic et al. studied 976 subjects in Belgium. They found that Airway resistance and specific airway conductance (sG_{AW}) measured by plethysmography are helpful factors in the diagnosis and differentiation of obstructive airway diseases, including CF (11). Our findings support the mentioned investigations, while further showing that outpatient antibiotic therapy can significantly improve this marker.

Another important finding of the present study was that the mean ± SD of RV in the studied patients, before the treatment was 224.87±87.42 % and after treatment was 219.49±74.28%. It means that our treatment significantly reduced RV (p value: 0.00). Analysis of data in male patients showed the same results. In females the mean ± SD of RV before and after treatment were 238.18±108.18 % and 242.39±74.60%, respectively; however, this result was not statically significant (p value: 0.08).

We also found that the outpatient treatment could increase TLC values significantly. The mean ±SD of TLC in all the patients prior to treatment was 99.92±12.92% which increased to 108.63±16.32 %, after that (p value: 0.00).

Pittman et al. in 2012 reported that following antibiotic therapy, pulmonary function test results undergo significant

changes in *infants* with CF exacerbation. They studied FVC, FEV (0.5), FEF(25-75), FRCpleth (Plethysmographic measurements of functional residual capacity), RV and RV/TLC parameters. They found that before antibiotic administration, infants had some significant degrees of obstructive disease and air trapping and after the treatment, all of the mentioned parameters improved significantly (12). Nicholson et al., in 2017, indicated that treatment of patients in acute exacerbation phase would significantly improve hyperinflation (RV/TLC), as well as the dyspnoea score (13). In other studies the association between hyperinflation and exercise capacity limitation have been described (14 and 15). Our findings are consistent with the above studies, as we demonstrated that RV and TLC of our patients significantly improved after the treatment. In addition, we had the advantage of treating *all* of our patients with oral antibiotics in an outpatient setting. Briggs et al., in 2012, showed that most of the orally treated patients in mild exacerbations did not need any IV course; and oral antibiotic therapy was effective (16).

5- CONCLUSION

In the current study, we showed that oral antibiotic therapy based on physician assessment and supportive cares in CF exacerbation could effectively improve values of FEV1, SRaw and TLC along with reducing RV values and air trapping. So, we highly recommend to the expert pediatricians dealing with these children, to keep the possibility of outpatient management, in their minds. In this way, the patients will be properly managed, while they get rid of disadvantages of hospitalization.

6- ETHICAL CONSIDERATIONS

This study was approved by the Research deputy and Ethics committee of the Tehran University of Medical Science. The ethics approval code is IR.TUMS.MEDICINE.REC.1396.4323. We also registered our manuscript in Iranian Registry of Clinical Trials. Trial registration number is IRCT20191112045413N2. We obtained a written informed consent signed by parents of all of our patients at the beginning of admission to the hospital.

7- Conflict of interest

None.

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