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Original Article

Electronic home monitoring of children with cystic fibrosis to detect and treat acute pulmonary exacerbations and its effect on 1-year FEV_1

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ABSTRACT

Background: We aimed to investigate the effect of the use of electronic home spirometry in children with cystic fibrosis (CF) on 1-year FEV_1 (% predicted, pp) change.
Methods: This is a randomised, one-year prospective study including children with CF between 6 and 18 years of age. Subjects were randomised into home spirometry group (HSG) and usual care group (UCG). Children in HSG performed two pulmonary function tests (PFT) per week. Data regarding acute pulmonary exacerbations (PEx) was obtained from patients' records. At baseline and 12th month, health related quality of life questionnaire for CF patients (CFQ-R) and lung clearance index (LCI) were performed.
Results: Sixty children were recruited with a median (IQR) age of 13.3 (11.4–15.4) years. Absolute change in FEV_1pp from baseline to 12th month as median (IQR) was +1% (-6.75–9.75) in HSG and -2.50% (-7.50–3.25) in UCG ($p = 0.10$). Sensitivity analysis including only adherent children in HSG ($n = 22$), yielded an increase of 5% (-3.50–12) in HSG and a decrease of 2.50% (-7.50–3.25) in UCG ($p = 0.009$). A total of 29 (96.7%) subjects in HSG and 23 (76.7%) in UCG had PEx ($p = 0.05$). Absolute change in median (IQR) $LCI_{2.5}$ from baseline to the 12th month was -1.6 [-2.9–0] ($p<0.001$) in HSG and -1.5 [-2.8-(-0.6)] ($p<0.001$) in UCG ($p = 0.94$). There was a significant increase in the social domain of the CFQ-R in HSG (from 59.1 to 76.2, $p = 0.01$).
Conclusions: Electronic home monitoring of children with CF by spirometry may result in improvement in lung function.

1. Introduction

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive, progressive disease and affects more than 100.000 people worldwide [1]. Acute pulmonary exacerbations (PEx) are frequent and major events in the lives of patients with CF. They may cause diminished lung function, worse health related quality of life, and shortened survival [2–4]. Pulmonary function tests (PFT), especially forced expiratory volume in 1 s (FEV_1), are the best objective clinical method in evaluating the lung health of people with CF [5]. As another method of PFT, lung clearance index (LCI) is a sensitive measure of ventilation inhomogeneity and has proven to be able to detect early lung diseases even in people with CF with normal spirometry measurements [6,7]. However FEV_1 is the most commonly used method and LCI is used for researches in our clinic.

People with CF may only contact their healthcare provider when their symptoms become severe. Longer time from symptom onset to exacerbation treatment was associated with worse treatment outcomes [8]. Approximately 25% of the subjects failed to return to their baseline lung function within three months after each exacerbation [8].

Studies also revealed that in people with CF home-based spirometry is feasible, safe, satisfactory and can detect PEx accurately at an early stage [9–13]. Furthermore, coronavirus disease pandemic (COVID-19) has changed the way of healthcare delivery. Telemedicine and remote monitoring have become a part of patient care [14].

Our hypothesis was that more PEx can be detected at an earlier stage

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by electronic home monitoring of FEV_1 and early treatment may allow a less decline in FEV_1 over 12 months than usual care group. To test this, we performed a prospective, randomised, controlled study of electronic home monitoring of FEV_1 for early treatment of PEx in children with CF. Our secondary aim was to detect the change in LCI and QoL.

2. Methods

2.1. Subjects and study design

This is a randomised, non-blinded, prospective, 12-month trial. At the time of study planning, 326 people with CF were followed up by five pediatric pulmonologists, four fellows, two CF nurses, one dietitian, and one physiotherapist in our center. People with CF were routinely seen quarterly by the team. Although there is a lack of standardization, 27 CF centers are following people with CF in Turkey. In our CF center, 161 children were between 6 and 18 years of age. Among them, children who could attend routine 3-month clinical visits regularly under pandemic conditions were evaluated for participation. Subjects meeting the inclusion criteria were recruited between November 2020 and June 2021. Children with CF between 6 and 18 years of age who could perform spirometry and had a smartphone were included in the study. Subjects with the following characteristics were excluded from the study: have a current PEx or had a PEx in the preceding 15 days; have other CF-related comorbidities like pulmonary hypertension and allergic bronchopulmonary aspergillosis (ABPA), which may affect lung function; be a candidate for lung transplantation; have atypical Mycobacteria and Burkholderia colonization that may make the matching difficult; and do not want to participate in the study. Eligible subjects were matched according to age, colonization status (Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus, methicillin-sensitive Staphylococcus aureus, Achromobacter xylosoxidans and Acinetobacter baumannii and no colonization), and the best FEV_1 pp of the previous year, and then randomised into two groups by simple randomisation as the home spirometry group (HSG) and the usual care group (UCG). Colonization was defined as being cultured in $\geq$50% of samples.

Both groups underwent normal clinical outpatient visits every three months and received usual daily treatments/airway clearance methods. All Turkish citizens are born with health insurance. Medications, including dornase alpha, hypertonic saline, vitamins, pancreatic enzymes, and antibiotics, except modulators, are covered by the insurance. In addition to routine therapy, the HSG group was asked to perform spirometry at home twice a week.

Written informed consent was obtained from the parents of all participants. The study was approved by the Ethical Committee of Marmara University School of Medicine (Protocol number: 09.2020.677).

2.2. Primary and secondary outcomes

The primary outcome was the 12-month change in FEV_1pp. Children in the HSG received a handheld spirometry (SpiroHome Personal, Inofab Health, Turkey). The SpiroHome device is a portable spirometry coupled with a dedicated smartphone application. The device communicates wirelessly via Bluetooth to the mobile application and results are transferred to the cloud system simultaneously. It measures all of the widely used spirometry parameters such as FEV_1, forced vital capacity (FVC) and peak expiratory flow (PEF) in addition to flow volume loops. The device was tested for accuracy, reproducibility and interdevice variability [15]. In this study, the clinical performance of the Spirohome was compared with a reference device, the EasyOne Air. A total of 48 children and adolescents performed spirometry with both devices. There was a strong correlation between the devices in the measurement of key pulmonary function parameters, including FEV_1 and FVC, with a Pearson's correlation coefficient of 0.99 and p values were $<$0.001 for both. Children in HSG were instructed on the correct use of their device by a CF nurse at enrollment and asked to perform PFTs on Wednesdays and Sundays at the same time of the day for 12 months. Reminder messages were sent to the participants from a WhatsApp group. The results of PFTs were evaluated by a registered CF nurse for a decline in FEV_1 from baseline weekly. Subjects with more than a 10% decrease in expected FEV_1pp were invited by phone to the CF center and evaluated by a pediatric pulmonologist.

Children in UCG were also asked to call CF nurses when they had unusual respiratory symptoms or an increase in their respiratory symptoms. Measurements of home spirometry were only used for the remote follow-up of subjects in HSG and were not interpreted in the analysis of the FEV_1 comparison of groups. In routine clinical visits, both groups performed conventional spirometry. PFT was measured using a spirometry (WinspiroPRO 2.8 MIR, Rome, Italy) in accordance with ERS/ATS standards. PFT was performed after applying a nose clip in an upright sitting position using the same device. Only results which met ERS/ATS standards for interpretation were included in the project for analysis [16].

The secondary outcomes were the relative change in FEV_1 pp, the number of PEx, days in hospital for PEx and days on oral antibiotics for PEx, time to the first PEx, time from the end of the first PEx to the onset of the second PEx, change in LCI, change in the health-related quality of life (QOL) questionnaire for CF (CFQ-R) patients and adherence to the study. Adherence to the home spirometry was defined as the completion of 70% of the measurements over 12 months. LCI and QOL questionnaire were performed at the beginning and end of the study.

A PEx was defined according to the modified criteria of Fuchs et al. which was used routinely in our clinical practice [17]. A recent change in at least two of the following was considered to be an indication of a PEx, which required extra antibiotic treatment: Change in sputum volume or color, increased cough, increased malaise, fatigue or lethargy, anorexia or weight loss, decrease in PFT by $\geq$10% or radiographic changes, increased dyspnea. The PEx was treated according to the Royal Brompton Hospital guideline for the care of children with CF. After antibiotic selection according to the colonization status, the treatment was given orally or inpatiently according to the clinical condition, in addition to increasing the frequency of airway clearance [18].

2.3. End-of-study questionnaire

At the end of the study, a questionnaire regarding the experiences with home spirometry was completed. On a 5-point Likert scale, parents and children were asked to rate the effectiveness and reliability of the device as well as their satisfaction and desire to continue using it.

2.4. Statistical analysis

The IBM SPSS Statistics (version 22.0 IBM Corp., Armonk, NY) software program was used to analyze the data. Categorical variables are presented as numbers (n) and percentages (%). Continuous variables are shown as medians with interquartile range (IQR) for the data that did not follow a normal distribution and are shown as means with standard deviation for the data with a normal distribution. Categorical variables were compared through the Pearson's chi-square and Fisher's exact tests. Continuous variables for two groups were compared with the Mann Whitney U test. Measurements of both spirometries were assessed using the Pearson correlation test. A p-value $<$0.05 was considered as significant.

3. Results

3.1. Baseline characteristics

We screened 76 eligible children with CF. Sixteen of them were excluded. Of them, 12 children were clinically unstable or on the transplant list, three children had atypical Mycobacteria or Burkholderia

colonization and one subject did not want to participate. The remaining 60 children were randomised into two groups as HSG and UCG. All of the participants have completed the study. The median (IQR) age was 13.1 (11.6–14.9) years in HSG and 14.0 (11.0–15.5) years in UCG ($p = 0.81$). The baseline characteristics are presented in Table 1. At the time of study, none of the children was on modulator therapy.

3.2. Primary outcome

Absolute change in FEV_1pp from baseline to 12th month as median (IQR) was +1% (−6.75–9.75) in HSG and −2.50% (−7.50–3.25) in UCG ($p = 0.10$). Sensitivity analysis of the primary outcome, including only adherent children in HSG ($n = 22$), yielded a statistically significant difference with an increase of 5% (−3.50–12) in HSG and a decrease of 2.50% (−7.50–3.25) in UCG ($p = 0.009$). The change in mean FEV_1pp of routine quarterly clinical visits is presented in Fig. 1.

3.3. Secondary outcomes

The relative change in FEV_1pp from baseline to 12th month as median (IQR) was +1.20% (−8.50–10.44) in HSG and −2.46% (−7.67–4.24) in UCG ($p = 0.11$). In the sensitivity analysis, including only adherent children in HSG, yielded a statistically significant difference with an increase of 5.56% (−3.33–13.50) in HSG and a decrease of 2.46% (−7.57–4.24) in UCG ($p = 0.01$).

A total of 29 (96.7%) children in HSG and 23 (76.7%) children in UCG had PEx during the study period ($p = 0.05$). Details regarding PEx during the study period are presented in Table 2.

The median (IQR) days of time to the first PEx were 67 (30–172) days in HSG and 144 (60–232) days in UCG ($p = 0.07$). The median (IQR) days from the end of the first PEx to the onset of the second PEx were 90 (28–120) days in HSG and 90 (57–139) days in UCG ($p = 0.57$).

There was a significant improvement in LCI in both groups. Absolute change in median (IQR) $LCI_{2.5}$ from baseline to the 12th month was −1.6 [−2.9–0] ($p<0.001$) in HSG and −1.5 [−2.8-(−0.6)] ($p<0.001$) in UCG. However the change in $LCI_{2.5}$ from baseline to the 12th month between HSG and UCG could not reach statistical significance ($p = 0.94$). The change in $LCI_{2.5}$ was moderately correlated with the 12-month change in FEV_1 pp in HSG (r: −0.41, $p = 0.02$) and not correlated in UCG.

Measurements of home spirometry and conventional spirometry in routine clinical visits were correlated. The mean (SD) FEV_1pp was 92.6 ± 12.9 in home spirometry and 87.0 ± 14.1 in conventional spirometry (r: 0.91, $p<0.001$).

All of the participants and parents of children younger than 14 years answered the CFQ-R at 0 and 12th months. There was a significant increase in the social domain of the questionnaire in HSG (from 59.1 to 76.2, $p = 0.01$). There was no other statistically significant difference.

Adherence to home spirometry measurement was 73.3% ($n = 22$). All children and parents completed the end-of-study questionnaire separately. The average scores of the questionnaire are presented in Fig. 2. Ten children (33.3%) and 15 parents (50%) responded that they wished to continue using the home spirometry device.

Table 1
Baseline characteristics.

	HSG ($n = 30$)	UCG ($n = 30$)	p value
Age, yr, median (IQR)	13.1 (11.6–14.9)	14.0 (11.0–15.5)	0.81
Sex			
- Male, n (%)	21 (70.0)	15 (50.0)	0.11
- Female, n (%)	9 (30.0)	15 (50.0)	
Nutritional status			
- Weight, kg, median (IQR)	41.5	46.0	0.35
- Height, cm, mean (SD)	(31.6–48.9)	(34.9–54.4)	0.90
- BMI, median (IQR)	151.0 (13.8)	150.5 (16.4)	0.04
	17.4 (15.9–20.6)	18.7 (17.4–21.6)	
Colonization status			
- Pseudomonas aeruginosa, n (%)	10 (33.3)	8 (26.7)	0.57
- MRSA, n (%)	3 (10.0)	4 (13.3)	1.00
- MSSA, n (%)	10 (33.4)	13 (43.4)	0.43
- Achromobacter xylosoxidans	0	1 (3.3)	1.00
- Acinetobacter baumannii	1 (3.3)	0	1.00
- No colonization, n (%)	6 (20.0)	4 (13.3)	0.49
FEV_1pp distribution, n (%)			
- 40 to <70%	2 (6.7)	2 (6.7)	
- 70 to <90%	10 (33.3)	7 (20.3)	
- ≥ 90%	18 (60.0)	21 (70.0)	
$LCI_{2.5}$, median (IQR)	10.0 (8.3–14.8)	10.7 (7.7–13.7)	0.67
Number of PEx in the previous 12 months/Number of children having PEx	8/8	14/8	0.70
- Treated IV, n	63/27	51/23	0.29
- Treated PO, n	71/27	65/23	0.53
- Total, n			

BMI: Body mass index; IV: Intravenous; MRSA: Methicillin-resistant staphylococcus aureus; MSSA: Methicillin-sensitive staphylococcus aureus; PEx: Pulmonary exacerbation; PO: Peroral.

4. Discussion

This prospective interventional study revealed that follow-up of children with CF with home spirometry has a positive effect on FEV_1 and PEx can be detected at an early stage. We also observed an improvement in $LCI_{2.5}$ in all subjects of the study. To our knowledge, this is the first study evaluating the long-term effect of home spirometry monitoring on LCI.

Higher lung function is associated with better quality of life and longer survival in people with CF. FEV_1pp, the most frequently used PFT parameter, is also a sign of better CF care [19,20]. A few studies have revealed that although home spirometry monitoring in people with CF may detect more PEx than in normal care, this may not have been associated with a positive effect on lung function measurements over the course of one year [10,11,21]. In a one-year multicenter study of home spirometry in 37 children with CF, subjects were asked to perform home spirometry thrice weekly for one year and it was found that the combination of home monitoring of FEV_1pp and respiratory symptoms can predict a PEx at an earlier stage, but they did not demonstrate the change in FEV_1 [10]. In the Nash et al. study, 88 adults with CF were recruited as home monitoring group by a home spirometry and routine care group equally and the home spirometry group was asked to perform spirometry twice weekly for a year. Although it was shown that more PEx were detected in the home monitoring group and most of these PEx being treated with oral antibiotics, FEV_1 did not significantly change over the course of the study [21]. Similarly, a randomised controlled study of Lechtzin et al. demonstrated that an intervention of home monitoring in adolescents and adults with CF was able to detect more PEx than usual care. It was a multicenter study including 267 adolescents and adults with CF (eICE study). It had a usual care arm with 132 subjects and an intervention arm with 135 subjects measuring home spirometry twice weekly as well as electronically recorded symptoms. They could detect more PEx but this could not result in a positive effect on lung function over one year [11]. In our study, we have shown a significant increase in FEV_1 in adherent children in HSG compared to UCG. To our knowledge, this is the first study demonstrating an increase in FEV_1 in children with CF who were followed up by home spirometry.

We hypothesized that the increase in FEV_1 could be related to many factors. First of all, the number of subjects with PEx, the total number of hospitalizations and oral antibiotics were higher in HSG compared to UCG. Even if experiencing numerous PEx is an important risk factor for decline in PFTs, there is evidence that CF programs with a focus on consistency and a low threshold for PEx diagnosis and treatment are able

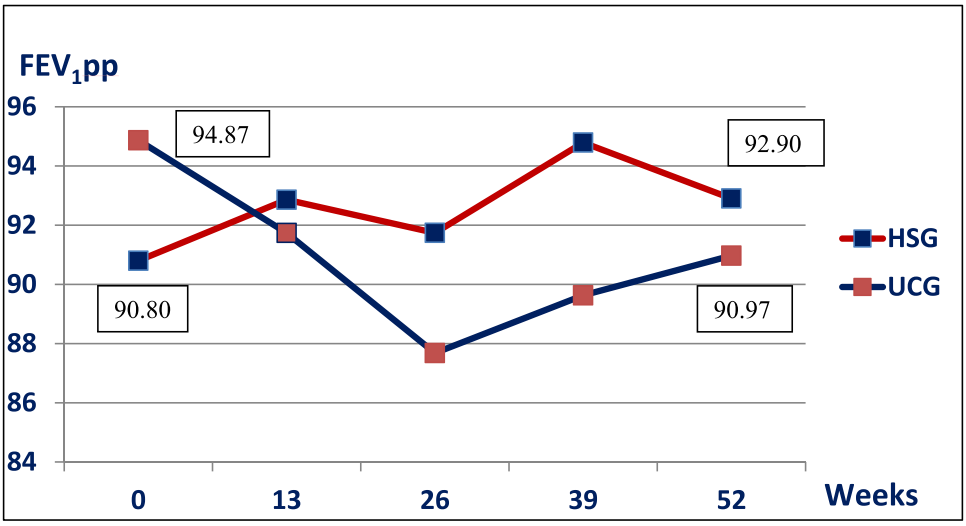

Fig. 1. The change in mean FEV_1pp in routine quarterly clinical visits in both groups.

Table 2
Summary of PEx during the study period.

	HSG (n,%)	UCG (n,%)	p value
Total number of subjects having PEx	29 (96.7)	23 (76.7)	0.05
Total number of PEx	77	57	0.08
Total number of oral antibiotics	62 (80.5)	49 (86)	0.28
Total number of subjects taking oral antibiotics	29 (96.7)	23 (76.7)	0.05
Total days on oral antibiotics	896	687	0.22
Total number of hospitalizations for PEx	15 (19.5)	8 (14)	0.13
Total number of hospitalized subjects	10 (33.3)	5 (16.7)	0.14
Total days in hospital for PEx	197	113	0.18

PEx: Pulmonary exacerbation.

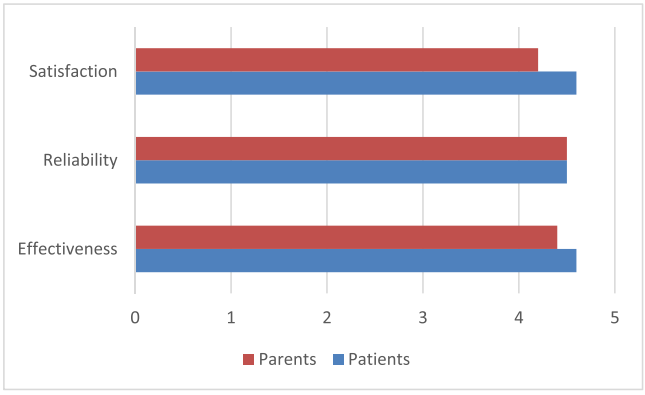

Fig. 2. The average scores of the end-of-study questionnaire.

to keep their patients' lung functions at a higher level [22–24]. Programs in the top decile for FEV_1pp had a high sensitivity to PEx symptoms and a propensity to initiate antibiotic therapy early and aggressively in response to clinical declines [24].

Secondly, the use of home spirometry might motivate subjects to adhere to their daily treatments, which may have contributed to the increase in FEV_1. Shakkottai et al. investigated the effect of weekly home PFT monitoring on medication adherence. The study included 39 people with CF aged 12–21 years. The mean medication possession ratio significantly increased [25]. Adherence to regular home spirometry measurements was 73% in our study, much better than in previously reported studies, in which adherence rates to home spirometry 1–3 times a week or even monthly were between 2 and 59% despite reminders [9–11,21,25–27]. In order to increase adherence to home spirometry measurements, we emphasized the importance of the measurements during face-to-face clinical visits and sent reminder messages on test days. Although we did not monitor the compliance to their daily CF treatments, we assume that home spirometry usage may lead to higher treatment compliance, which may have contributed to the increase in FEV_1 level.

To our knowledge, this is the first study evaluating the effect of home spirometry on LCI in people with CF. We observed a significant improvement in LCI in both groups. Although change in FEV_1 in HSG was significantly higher compared to UCG, LCI changes were not different in both groups. Sonnevel et al. reported previously published data regarding the LCI response as an outcome measurement in PEx treatment in pediatric and adult population with CF. Similar to our study, they found that the change in LCI was not correlated with the change in FEV_1 in almost half of the subjects [28]. LCI and FEV_1 measure different aspects of lung physiology. FEV_1 mainly reflects large airway function and will be affected by mucus accumulation and air trapping. In contrast LCI is affected by heterogeneities at all levels of the airway tree, mostly the periferal airways. Although all these factors can be improved by PEx treatment, the predominantly affected lung component of patients may vary, which can partly explain the discordance between FEV_1 and LCI.

Digital technologies are extensively used in many portions of life and the importance of them in the field of health care is being more recognized. Additionally, the COVID-19 pandemic has given rise to a dramatic increase in telehealth. These developments have led the World Health Organization, the Cystic Fibrosis Foundation and many other organizations to publish a strategy on digital health [14,29,30]. Home spirometry devices are now being used widely in CF and other chronic lung diseases, and it is likely to continue even after the pandemic is over. Although it is not yet within the scope of reimbursement, 50% of the parents and only 33% of children stated that they would like to continue using the device. Personal communication with subjects revealed that home spirometry measurement was perceived as another burden for CF care and a threat for possible hospitalization.

This study has some limitations. Due to the nature of the study design, it could not be blinded. This is a single center study with small sample size. Multicenter implementation of this process including a wider variety of people with CF may confirm the efficacy of home spirometry monitoring on lung function. The other limitations are the inability to control technique in home spirometry monitoring, the inability to measure medication use, and the frequence of airway

cleaning. Strengths of our study are: [1] it was randomised and controlled; [2] longitudinal follow-up of one year; [3] the device does not require a computer or cable and transfers data directly via bluetooth; and [4] the use of a definition for PEx diagnosis, limiting overdiagnoses of PEx.

As a conclusion, the usage of home spirometry with high adherence may allow better lung function in children with CF. Home spirometries can also be effectively used in low resource settings and may have beneficial effects on lung function, quality of life and survival.

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CRediT authorship contribution statement

Muruvvet Yanaz: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Visualization, Writing – original draft. **Cansu Yilmaz Yegit:** Conceptualization, Investigation, Resources. **Aynur Gulieva:** Conceptualization, Investigation, Resources. **Mine Kalyoncu:** Conceptualization, Investigation, Resources. **Merve Selcuk:** Conceptualization, Investigation, Resources. **Burcu Uzunoglu:** Conceptualization, Investigation, Resources, Data curation. **Gamze Tastan:** Conceptualization, Investigation, Resources. **Almala Pinar Ergenekon:** Conceptualization, Investigation, Methodology. **Yasemin Gokdemir:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Ela Erdem Eralp:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Fazilet Karakoc:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Bulent Karadag:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

None.

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