The effects of aerobic exercises compared to conventional chest physiotherapy on pulmonary function, functional capacity, sputum culture, and quality of life in children and adolescents with cystic fibrosis: a study protocol for randomized controlled trial study

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Abstract

Background

Cystic Fibrosis (CF) is an autosomal recessive disorder caused by abnormal function of the chloride ion channel, and characterized by pancreatic insufficiency, and chronic endobronchial airway infection. Pulmonary dysfunction is very common and could lead to a reduction in the quality of life. Airway Clearance Techniques (ACT) and physical exercises are introduced as one of the main components of treatment. Therefore, it will be of interest to examine the effect of aerobic exercises compared to Conventional Physiotherapy (CPT) on pulmonary function, exercise capacity, functional capacity, sputum culture, and quality of life in patients with CF.

Methods

Thirty Patients with CF will participate in a double-blind parallel controlled trial containing 18 sessions of treatment. Group A consists of CPT and placebo aerobic exercise, and group B includes aerobic exercise and placebo CPT. Pulmonary function, functional capacity, sputum culture, and quality of life will be evaluated with a spirometry test, 6-minute walk test (6MWT), sputum culture test, and the Cystic Fibrosis Questionnaire-Revised (CFQ-R), respectively before and after the intervention.

Discussion

We will evaluate and compare the effectiveness of aerobic exercises and conventional chest physiotherapy on pulmonary function, functional capacity, sputum culture, and quality of life. Comparing these two treatment patterns can contribute to a better understanding of the effectiveness. Therefore, if there is a significant difference between two treatments, the superior treatment will be prioritized clinically.

Trial registration:

This trial is registered at https://www.irct.ir, under trial number IRCT20210505051181N5, approved at 2/19/2023.

Introduction

Background and rationale {6a and 6b}

Cystic Fibrosis (CF) is one of the most common of autosomal recessive diseases (1). Pulmonary complications of CF are one of the most common causes of death with 60% mortality, especially in children and adolescents (1, 2). Despite the lower prevalence of this disease in the Asian continent (1 per...
35,000 births), the number of patients has been increasing over the last two decades (1). The CF affects various systems with more involvement in the respiratory system, causing very viscous, hard, and sticky mucous secretions that accumulate in the excretory pathways (1). This makes the basis for inflammation, recurrent infections and tissue fibrosis (3, 4). With every episode of pulmonary infection, a high percentage of patient's lung function is irreversibly lost (4). As a result, the quality of life is reduced and can be very disruptive in daily activities (1–3, 5). Therefore, choosing the appropriate treatment is important in treating these patients and reducing the disease burden (3, 6). Airway clearance techniques (ACT) and physical exercise are introduced as one of the main components of treatment (1, 3, 7, 8).

Conventional chest physiotherapy (CPT) is the oldest forms of ACT that was introduced in 1940’s (9) and is recommended as the standard treatment that can be performed by all people of all ages (10). Based on the results of most of studies, including guidelines and systematic reviews, there is no meaningful difference between the different ACTs (including CPT, active cycle of breathing technique (ACBT), autogenic drainage (AD) and oscillating positive expiratory pressure (OPEP) devices). They all lead to more clearance of the produced sputum, reducing the recurrence of pulmonary infections and slowing the progression of lung destruction. This in turn improves lung function and increases the quality of life for patients (3, 7, 8, 11–16). Choosing the best method depends on the patient’s ability to perform, preference and available facilities (7).

Aerobic exercises are another important treatment option, as they increase the endurance and cardiopulmonary fitness, aerobic capacity, mental health and quality of life (17–19). In addition, it is hypothesized that due to the increase in the respiratory rate and volumes and more passage of substances across the respiratory membranes and resultant increased ventilation, this treatment can also have significant effects on the evacuation of secretions (9, 20–23). In addition to softening and moistening respiratory secretions, it also increases cough stimulation in patients, and has been very effective in draining respiratory mucus (18, 20, 23, 24). Limited studies also demonstrate its positive effects on respiratory infections (25, 26).

Hebestreit et al., in a randomized controlled trial study, investigated the effects of 1-year semi-supervised physical exercise (27). The hypothesis was that an exercise program of 3 hours per week can increase the pulmonary function level (forced expiratory volume in 1st second- FEV1) of CF patients and its effects can be maintained for 6 months. The results demonstrated a significant FEV1 percent predicted increase in the control group, compared to the exercise group (2.70% predicted [95% CI, 0.13–5.26]; P = 0.04). Patients in the exercise group reported an increase in their level of daily activities (8.1% predicted [95% CI, 3.6–12.6]) and exercise capacity (4.5% predicted [95% CI, 1.0–8.0]). These effects were maintained for 1 year. Dweyer et al, in a randomized cross-over study compared the effects of a treadmill, airway clearance (PEP), and control on sputum clearance and patient symptoms (18). Based on the results, mucus clearance was higher in the PEP group (MD − 7%, 95% CI − 6– −8; p < 0.001), treadmill exercise (MD 3%, 95% CI 2–4; p < 0.001), and the control group, respectively. The number of coughs did not show a significant difference between the 3 groups, rather more apparent in the PEP group (MD 69, 95%CI 33–105; p < 0.01). Dweyer et al, in another cross-over study, compared the effects of treadmill exercise, and
flutter on respiratory flow, characteristics of expectorated sputum, and clinical signs of subjects (28). The maximum expiratory flow (MEF) in the treadmill (MD 1.68 ± 0.51, 95% CI; p < 0.01) and flutter (1.53 ± 0.25, 95% CI; p < 0.01) groups was higher. The mechanical impedance of the expectorated sputum of these two groups was not different. The number of coughs in the flutter group (MD 24 (18–34), 95% CI; p < 0.01), exercise (MD 4 (1–9), 95% CI; p < 0.01) and the control group was higher, respectively. Therefore, it was demonstrated conclusively that both treatments equally helped to clear the airways more effectively.

CPT is still the standard and most widely used method for children and adolescents with CF; because teaching other ACT methods has proven to be difficult for them to follow, and their effectiveness depends on correct learning and implementation processes; However, due to the inconvenience, time-consumption, and dependence of CPT on others, nowadays it is not uncommon, for most patients and even their families to prefer the alternative methods (7). Also, aerobic exercise is readily available activity that is practicable and clinically recommended (20).

Several studies have investigated the effectiveness and quality of the implementation of unsupervised interventions at home by patients or their parents (9, 29, 30), with results demonstrating that treatment adherence is 30% (9). Study results reveal that unsupervised treatment has fewer positive effects compared with supervised treatment (25, 31, 32). Numerous studies, including systematic reviews (alluding to the controversy in the results of aerobic exercises and the low methodological quality of these studies) have mentioned the need for further investigation in this field so that it is can be credible to recommend the possibility of using aerobic exercises as a viable alternative and independent ACT (17, 20, 33–35).

To the best of the authors’ knowledge, a study comparing aerobic exercises with CPT with high quality and precise design has not yet been investigated. Therefore, the aim of this study is to compare the effect of aerobic exercises compared to CPT on pulmonary function, exercise capacity, functional capacity, sputum culture, and quality of life in patients with CF. This is so that if significant changes are observed due to aerobic exercises compared to CPT, clinically, aerobic exercises can be recommended among treatment priorities.

**Objectives and hypotheses (7)**

In this trial we aim to include 30 children and adolescents CF patients into a 1:1 randomized controlled trial study. We will compare the effects of Conventional Chest Physiotherapy (CPT) and sham aerobic exercise in one group and aerobic exercise and sham CPT in the other group. The primary objective is to evaluate the effects of the 18-session aforementioned treatments on pulmonary function (FEV1) and functional capacity in children and adolescents with CF. The secondary objective is to assess the changes in sputum culture, pulmonary function (FVC) and quality of life of CF patients.

We hypothesize that there will be an increase by at least 7.1% in FEV1% percent predicted (minimally clinical important difference (MCID) considered for FEV1 (36)), a significant increase in the amount of
FVC, at least 33 meters increase in the distance covered in 6MWT (MCID considered for 6MWT (36)), a significant increase in the percentage of negative sputum culture test and reduction of colony count tests after 6 weeks of aerobic exercise and CPT in CF patients, and a significant difference between the two groups. Also, CFQ-R quality of life questionnaire score is expected to have a significant increase of at least 11.4 points in the physical domain, 7.3 points in the respiratory domain (MCIDs considered for CFQ-R (36)) and in the overall score.

**Trial design {8}**

The current project is a double-blind 1:1 randomized controlled trial study designed to investigate and compare the effects of aerobic exercises and CPT in two parallel groups; group A consisting of CPT plus sham aerobic exercise, and group B consisting of aerobic exercise and sham CPT. This study will be conducted at the CF specialized clinic of the Children's Medical Center Hospital, Tehran, Iran; children and adolescents with confirmed diagnosis of CF will be randomly allocated in either group A or B.

Primary data-points including FEV1, 6MWT, and secondary outcomes including sputum culture test (key secondary), FVC and CFQ-R quality of life questionnaire will be assessed before and after treatments. It is expected that both treatments will have meaningful effects on aforementioned variables and if significant changes be observed due to aerobic exercises compared to CPT, clinically, aerobic exercises will be recommended among treatment priorities.

**Methods: Participants, interventions, and outcomes**

**Study setting {9}**

Data will be collected at the CF specialized clinic of the Children's Medical Center Hospital, Tehran, Iran. Patients diagnosed with CF will be referred by pediatric pulmonologist (MME) or called among the previous files available.

**Eligibility criteria {10}**

Table 1 summarizes the inclusion and exclusion criteria for the groups. Participants must meet all the eligibility criteria to be included.

[Table 1 about here]

**Interventions {11a}**

The treatment session will commence thirty minutes after the first examination. Group A will first include the main treatment of CPT and then a placebo of aerobic exercise; group B will first includes the main
treatment of aerobic exercise and then a placebo of CPT (the inverse of Group A). The study will be conducted over 6 weeks, 3 times a week, with a total of 18 sessions. The duration of the entire treatment session will last approximately 70 minutes.

**Group A (CPT and sham aerobic exercise)**

At first, the participants will be placed in six standard postural drainage positions for total 30 minutes (appendix, supplemental Fig. 1- A to F). Manual percussion and vibration will be performed on draining segments, in each position for 3–5 minutes. After completing the previous steps, the patient will be asked to sit down and cough for 1–2 minutes to expel the extracted secretions. In the following, the placebo aerobic exercise will be applied using a motorized stationary bike in two 15-minute sections (appendix, supplemental Fig. 2). Between the two parts, 1–2 minutes of time will be allocated for rest. Throughout the exercise, the heart rate and percentage of arterial oxygen saturation (SpO2) of the patients will be monitored by a pulse oximeter. In this group, in order to eliminate the aerobic effects of the exercises, based on the method of previous studies (38), increasing the respiratory demands and breathing ventilation will be avoided until the end of the study. Therefore, the heart rate of the subject does not exceed 40% of HRmax during 30 minutes (39). The total time of the exercises is 30 minutes, and at the end, 1–2 minutes will be given for coughing, if needed.

**Group B (Aerobic exercise and sham CPT)**

Progressive aerobic exercises will be conducted in two parts; the first will be 15 minutes on the treadmill and then a further 15 minutes on a stationary bike. Between the two sets rest will be given for 1–2 minutes. A warm up of 3 minutes with a gradual increase in speed will take place, and then 24 minutes of aerobic exercise with determined intensity (12 minutes on the treadmill and 12 minutes on a stationary bike), and finally a 3-minute cool-down with a gradual decrease in speed (appendix, supplemental Fig. 3-A to C).

Throughout the training, the heart rate and SpO2 of patients will be monitored by a pulse oximeter. If there is a sharp drop in SpO2 below 85%, the heart rate is disproportionate to the conditions, symptoms of severe shortness of breath or any other warning signs appear, the exercise will be stopped. During 24 minutes of aerobic exercises, the intensity of the exercise will be controlled through the heart rate of the patients (table 2).

[Table 2 about here]

To perform postural drainage, in order to remove the effect of gravity, only 2 positions of supine and prone without inclination will be used; the treated areas and procedure will be similar to group A. In order to eliminate the effect of manual percussion, these strikes will be done very gently with pressure just like touching the skin. In order to eliminate the effects of vibration and pressure, hands will be placed on the desired areas and no vibration or pressure will be applied during exhalation. The total duration will last approximately 30 minutes. At the end, 1–2 minutes will be allocated for any coughing, if needed.
Criteria for discontinuing or modifying allocated interventions \{11b\}

The medical recommendations of individuals, such as drug treatments and airway clearance methods, will not be changed. Due to the risk of cross-infection, two infected patients will not be in the same environment at the same time (3). Before the treatment, participants are asked to use their 7% sodium chloride nebulizer at home to prepare the airways (40).

Strategies to improve adherence to interventions \{11c\}

To improve patient motivation, the comprehensive rehabilitation protocol will be offered completely free of charge, ensuring a seamless connection between the patients and their dedicated team of healthcare professionals including the physiotherapist (NH) and physicians. This regular contact will enable patients to promptly communicate any symptoms they may experience.

Relevant concomitant care permitted or prohibited during the trial \{11d\}

One week before the treatment starts and the days between treatment sessions, sports activities will be replaced by ACBT. The ACBT implementation is checked by the physiotherapist. The steps to implement the technique are breathing control, chest expansion, and forced expiration technique (FET) (11).

Outcomes \{12\}

All outcomes are measured on two measurement time points: at baseline, and after 6 weeks.

Primary outcomes

Pulmonary function (FEV1): FEV1 will be assessed objectively using a spirometry test (appendix, supplemental Fig. 4). After recording a maximum of 8 trials, the maximum values recorded in liters and the predicted percentage will be reported as results. The minimal clinically important difference (MCID) for FEV1% in CF has been reported as 7.1% (36).

Functional capacity: 6MWT will be performed based on the recommendations of the ATS Association (41). A 22.5 meters corridor, in an enclosed space and flat surface, is marked by two cones. Patients will be asked to walk as fast as they can within 6 minutes and cover the greatest possible distance between the two points without running. In the end, the distance covered in 6 minutes will be measured as the test result. The MCID for this test in patients with CF has been calculated to be 33 meters (36).

Key secondary outcome

Sputum culture: The test method will be based on the study of Marguet et al. (42). Two respiratory mucus sampling methods are used according to the patient’s ability (expectorated sputum/ swab method). The obtained samples will be sent to the laboratory within 2 hours. The main and common pathogens of CF, Pseudomonas Aeruginosa, Staphylococcus Aureus and Burkholderia Cepecia are cultured on the samples. The culture test will be positive if pathogen culture is observed in the sample. In addition, in
cases where the culture test is positive, the microbe colony count is also done and its amount is reported qualitatively (low/medium/high).

**Secondary outcomes**

Pulmonary function (FVC): FVC will be measured through spirometry test, the same as FEV1.

Quality of life (CFQ-R): Quality of life will be subjectively assessed by the Persian version of the Cystic Fibrosis questionnaire-revised (CFQ-R) (43, 44). This questionnaire examines different domains (physical functioning, vitality, emotional state, social functioning, role functioning of the individual, body image, eating disorders, treatment burden, general perception of health, respiratory, and digestive symptoms) affecting the quality of life of the person in the last 2 weeks and has been prepared in 3 versions according to the age of the patient. The differing versions are for:

1. Children 6 to 13 years old
2. Parents of above aged children
3. Adults 14 years old and older

The scale of answering questions is a 4-point scale. Total points are calculated and standardized in the range of 0 to 100. The closer the final score is to 100, the higher the quality of life. The MCID for the physical domain is 11.4 points increase and for the respiratory domain, 7.3 has been calculated (36). Validity and reliability of the Persian translated version of the CFQ-R has been evaluated by S. Talebi et al. The Cronbach-alpha for the CFQ-R was 0.65–0.91 for children and parents version, and ≥ 0.70 for adult version, showing good internal consistency.

**Other variables**

In addition to the aforementioned outcomes, demographic and physiological variables such as age, sex, height, weight, medication history, physical activity level, and history of performing ACTs will be measured.

**Participant timeline {13}**

Participant timeline is presented in Fig. 1 and study's time schedule is presented in table 3.

[Figure 1 about here]

[Table 3 about here]

**Sample size {14}**

A total sample size of 30 children and adolescents from a pediatric center was determined. This is based on a randomized controlled trial study by Sosa et al. (37). Using power analysis, the required sample size with a power of 0.8 and an α of 0.05 and taking into account 30% dropout probability in each group, the number of 14.3 patients in each group was calculated. Assuming a large effect size, we anticipate recruiting 15 participants in each group for the study.
Recruitment {15}

In order to reach the target sample size, the pediatric pulmonologist from CF specialized clinic will refer patients diagnosed with CF to the rehabilitation clinic of the Children's Medical Center Hospital. Patients will enter the study based on the eligibility criteria. In addition, patients will be called among the previous files available at the center.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be randomly allocated to intervention groups A, and B, in a 1:1 ratio, using block balanced randomization method.

Allocation concealment {16b}

The randomization process was done by a statistician (MP) before the start of the study. After the initial evaluation of participants by the examiner, who has enough experience and knowledge to do it, sealed numbered envelopes, corresponding to the sequential number of each person entered into the study, will be presented and the therapeutic intervention will be adjusted based on the letters inside the envelopes. The examiner and participants will be unaware of the letters inside the envelopes until the end of the study.

Implementation {16c}

Treatment will be administered by a physical therapist who has sufficient experience and knowledge to perform it.

Assignment of interventions: blinding

Who will be blinded {17a}

This study will be conducted as a triple-blinded study. The patients, outcome assessor, and the statistician will be provided with information about the treatment process. However, they will remain unaware of the specific allocation throughout the study.

When unblinding is permissible {17b}

Throughout the study, there will be no permission to reveal the allocation to either the outcome assessor or the patients. However, once the study is completed, the patients will be informed about their group allocation.

Data collection, management, and analysis: data collection methods
Plans for assessment and collection of outcomes {18a}

Outcomes are assessed at two time points, at baseline, and after treatment sessions, by the blinded examiner who has enough experience and knowledge to do it. Also, the demographic data will be gathered by the examiner in the first session. The Persian version of CFQ-R questionnaire used for quality of life assessment has been validated by S. Talebi et al. and the Cronbach-alpha for the CFQ-R was 0.65–0.91 for children and parents’ version, and ≥0.70 for adult version, showing good internal consistency (43, 44). The questionnaire forms can be accessed through the supplementary file 1.

Plans to promote participant retention and complete follow-up {18b}

Participant retention and complete follow-up are promoted by the monitoring of physical therapist. In case of withdrawal of patients from the study, their data will be counted as drop-outs.

Data management {19}

Throughout all stages of the trial, utmost care will be taken to ensure the security and confidentiality of participants’ personal information. All participant data, including reports, data collection, process details, and administrative forms, will be stored in lockable file cabinets located in restricted-access areas. These documents will be identified solely by a coded ID number, maintaining anonymity. Instead of using names, the participant's unique number identifier will be utilized in all data records. Forms, lists, logbooks, appointment books, and any other materials connecting participant ID numbers to identifiable information will be kept in a closed, separate file within a restricted zone. Only the primary investigator will have knowledge of the participants’ names associated with their respective numbers. To enhance data management, all collected data will be converted into electronic format and securely stored in password-protected files at the main study centers where the data originated. Access to this data will be strictly limited to the research team. Personal data will be stored separately from other information, treated as highly confidential, and accessible only to specifically authorized research team members. It will not be shared with any external parties, ensuring its complete privacy.

Statistical methods for primary and secondary outcomes {20a}

Data will be analyzed using Stata version 16. The normal distribution of data will be analyzed by the Shapiro-Wilk test. If the distribution is normal, parametric tests will be used for analysis before and after the intervention. To determine the homogeneity of variances (i.e., variances approximately equal across groups), Levene's test will be employed. If the variance is equal, the analysis of covariance (ANCOVA) will be used. The covariance variable in this test will be the initial data values before the intervention. The significance level of the tests is set at 0.05. In addition to the significance index, the effect size index is also used by Cohen's d method to compare two treatment methods for each variable. Therefore, the effect of the intervention on each of the dependent variables is determined, regardless of the sample size.
According to the new interpretation presented, the effect size can be divided and interpreted as follows: (from 0.01 to 0.2, very small), (from 0.2 to 0.5, small), (from 0.5 to 0.8, moderate), (from 0.8 to 1.2, large), (from 1.2 to 2, very large) and (more than 2, very large) (45).

**Methods for any additional analyses {20b}**

It is not considered.

**Methods in analysis to handle protocol non-adherence and statistical methods to handle missing data {20c}**

In order to increase adherence, patients are contacted weekly and given prizes. Missing data will be disposed of with the Multiple Imputation (MI) method.

**Data monitoring**

**Composition of the data monitoring committee, its role, and reporting structure {21a}**

Due to the absence of anticipated adverse outcomes, such as potential temporary soreness following the exercises, no data monitoring committee has been formed.

**Interim analyses and stopping guidelines {21b}**

It is not applicable.

**Adverse event reporting and harms {22}**

At the end of the study, a questionnaire will be completed by patients or their parents to evaluate any unwanted side effects that may have occurred during the study and are reported in the order of prevalence. The adverse events most frequently reported are summarized in table 4 and the adverse events questionnaire is provided in supplemental file 2.

[Table 4 about here]

**Auditing {23}**

There will be no auditing trial in this study.

**Ethics and dissemination**

**Research ethics approval {24}**
This study’s ethical approval was obtained from ethical research committee of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.REC.1401.919).

**Protocol amendments** {25}

Any change in the study plan requires the approval of the Ethical Committee.

**Consent or assent** {26a, b}

The informed consent form will be created following the guidelines provided by the Ethics Committee of Iran University of Medical Sciences. The hospital’s secretary will be in charge of collecting the consent form from the patients, their parents, or caregivers. Before signing the consent form, all eligible patients or their parents will be fully informed about the interventions and possible adverse events. For more information regarding the consent form, please refer to supplemental file 3.

**Confidentiality** {27}

The data of all patients will be stored and archived in a strictly confidential manner throughout all stages of the trial. The confidentiality of the data will be safeguarded not only during the trial but also after its completion.

**Declaration of interests** {28}

Declaration of interests {28}
This study has no declaration of interests.

**Ancillary and post-trial care** {30}

It is not applicable.

**Dissemination policy** {31a, b, c}

Upon the completion of the study, all collected data will undergo statistical analysis and subsequently be published in a peer-reviewed journal. Additionally, the findings will be presented at appropriate conferences. Participants will be given the opportunity to obtain a copy of the scientific publication(s) containing the complete, de-identified dataset.

Informed consent materials {32}
The consent form items have been specifically developed for participants who speak Persian, incorporating valuable suggestions obtained from the website of the Ethics Committee of Iran University of Medical Sciences.

**Biological specimens (33)**

Since the study does not involve the collection of biological specimens, there is no requirement for additional consent provisions.

**Discussion**

The present study will investigate the effect of aerobic exercises compared to conventional chest physiotherapy on pulmonary function, functional capacity, sputum culture, and quality of life in patients with Cystic Fibrosis.

Based on previous studies, respiratory problems, are the most common and important symptoms following CF (1). Some investigations reported a reduction in patients’ quality of life and spending a lot of time and money on treatment because of respiratory problems (1, 3). Other findings revealed positive effects of various types of ACTs on patients’ pulmonary function (7, 11–15). In a comparison between vigorous physical exercises and maintaining the previous physical activity level as a control, after 6 months of partially-supervised training sessions, a significant increase in exercise capacity was observed (27). Additionally, based on the results of systematic reviews, because of the low quality of the studies, no definite opinion has been made about the effects of physical exercises (7, 35). However, there is a lack of study that evaluated the effect of exercises on pulmonary function and quality of life, and the most positive effects of exercises have been seen on maximum aerobic capacity (35).

To the best of author knowledge, the studies conducted in the field of physical exercises are very limited, which indicates a need for more studies with higher methodological quality to be carried out in order to facilitate a commentary on the effect of physical exercises as ACT. In addition, no studies have evaluated the effects of supervised aerobic exercises compared to conventional chest physiotherapy on the most important health indicators of CF patients, including FEV1.

The main result of this study will explore and discuss about the question of what is the effect of supervised aerobic exercises on pulmonary function, functional capacity, sputum culture and quality of life? If there is a significant difference between the two treatments, one of them can be prioritized clinically.

The strength of our study is the measurement of pulmonary function and quality of life. The study will be double blinded RCT, and performed under the complete supervision of the physiotherapist. The duration of the treatment is 6 weeks, which is suitable for measuring the medium-term effects of the treatment. Patients' aerobic exercises will be as progressive as possible according to their condition. Among other
strengths in this study is the use of multiple clinical, functional, laboratory, and self-report variables at the same time so that treatment results can be discussed in a wider dimension.

Our study will have some limitations; the main limitation of this study is that children and adolescents (ranging 6 to 18 years) will be included, thereby, the generalizability of data is limited. In addition, due to the lack of access, there is a limitation in the sample size and a lack of follow-up in our study.

**Trial status**

The current protocol version is version 1 from July 23, 2023. Recruitment and enrolment of participants started on July 23, 2023. Expected recruitment end date is January 20, 2024 when the planned sample size is achieved.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CF</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiratory volume in 1st second</td>
</tr>
<tr>
<td>ACT</td>
<td>Airway clearance technique</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>CPT</td>
<td>Conventional chest physiotherapy</td>
</tr>
<tr>
<td>PEP</td>
<td>Positive expiratory pressure</td>
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<tr>
<td>6MWT</td>
<td>6-minute walk test</td>
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<tr>
<td>MCID</td>
<td>Minimally clinical important difference</td>
</tr>
<tr>
<td>CFQ-R</td>
<td>Cystic fibrosis questionnaire-revised</td>
</tr>
<tr>
<td>FET</td>
<td>Forced expiration technique</td>
</tr>
<tr>
<td>ACBT</td>
<td>Active cycle of breathing technique</td>
</tr>
<tr>
<td>MI</td>
<td>Multiple Imputation</td>
</tr>
<tr>
<td>OPEP</td>
<td>Oscillating positive expiratory pressure</td>
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<tr>
<td>HRmax</td>
<td>Maximum heart rate</td>
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</table>

**Declarations**

**Ethics approval, consent to participate and confidentiality**

This study's ethical approval was obtained from ethical research committee of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.REC.1401.919). Any change in the study plan requires the approval of the Ethics Committee. The informed consent form will be created following the guidelines provided by the Ethics Committee of Iran University of Medical Sciences. The hospital's secretary will be in charge of collecting the consent form from the patients, their parents, or caregivers. Before signing the consent form, all eligible patients or their parents will be fully informed about the interventions and possible adverse events. The data of all patients will be stored and archived in a strictly confidential manner throughout all stages of the trial. The confidentiality of the data will be safeguarded not only during the trial but also after its completion.

**Consent for publication**

Not applicable.
Availability of data and material

The final trial dataset will be accessible by sending a justifiable email to the corresponding author (MK).

Competing interests

The authors declare that they have no competing interests.

Funding

This study will be implemented under the supervision of School of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran; although the mentioned center has no role in the study design, data collection, data analysis, data management, data interpretation, and the dissemination of the study results. All authors declare that they did not receive any funding for this protocol.

Authors’ contributions

NH: project conductor, data curation, and writing original draft. MK: conceptualization, methodology, supervision, and drafting the article. SS: methodology, review, and editing. MRP: methodology, supervision; review, and editing. AE: methodology, supervision; review, and editing. MRME: methodology, project administration, patient recruitment, review, and editing. All authors have read and approved the final manuscript.

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References


Tables
Table 1 to 4 are available in the Supplementary Files section.

Figures
Figure 1

Patient timeline

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfile1.pdf
- supplementaryfile2.pdf
- supplementaryfile3.pdf
- tables.docx
- SPIRITfillablechecklist15Aug2013.doc
• Appendix.docx