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TRIAL PROTOCOL

Tittle:
Effects of music therapy as complement of chest physiotherapy in patients with cystic fibrosis

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Objective: To develop a strategy based on music therapy as adjunct to daily chest physiotherapy in children with cystic fibrosis and to evaluate its effects.

Study design: Interventional - randomized controlled trial. Single center: Unit of Pediatric Pulmonology, Malaga Regional Hospital.

Disease or disorder under study: Cystic fibrosis.

Participants: Children between ages of 2-17 from the Pediatric Pulmonology Unit at Malaga Regional Hospital. The sample size determined in each group is 13 participants. A total of 39 participants are necessary.

Total study period: Two years.

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BACKGROUND

Cystic fibrosis (CF), is a rare, chronic, multisystemic disease that greatly affects the quality of life. A progressive lung dysfunction and its clinical manifestations are found in 95% of patients (CFF, 2014). These clinical manifestations are mainly related to morbidity and mortality (Alexander et al, 2014, CFF, 2014). Thus, the decrease in lung capacity and its consequences contribute to a degeneration of lung tissue, being ultimately the lung transplantation the only solution (Prados et al, 2000, CFF, 2014). Therefore, it is essential to establish an adequate treatment that prevents the progression of the lung disease. Chest physiotherapy (CPT) is one of the main approaches used to improve airway clearance, being essential in the maintenance of pulmonary function in CF due to the excess of respiratory secretions in these patients (McIIwaine et al, 2014).

Chest physiotherapy treats bronchial obstruction through airway clearance techniques administration such as deep breathing, huffing, coughing, percussions or vibrations (Pisi and Chetta, 2009; Main et al, 2011; CFF, 2014). The CPT is prescribed daily, requiring a significant commitment of time and energy for children and family members, what complicates CPT adherence (Modi & Quittner, 2006) and reduces its benefits (Sabaté, 2003; Goodfellow et al. , 2015).

Music exerts a motivational role in chronic diseases leading to psycho-emotional improvement (Le Roux et al, 2007). Music therapy (MT) interventions are usually part of integrative strategies to ameliorate some physical and/or psycho-emotional consequences in lung diseases, case of chronic obstructive pulmonary disease (Bausewein et al, 2013; Panigrahi et al, 2014). Patients reach emotional positive states reducing anxiety and depression with MT (Canga et al, 2015). In this sense, there are few music therapy interventions in CF (Goldbeck et al, 2014; Irons et al, 2014). Recently, it has been described that a carefully selected motivational music can lead to positive affective response during exercise in CF children aged from 8 to 18 (Calik-Kutukcu et al, 2016). There is only one study in CF infants and children under 2 years of age where, an appropriate music created specifically for CPT, helps to establish CPT as a routine by converting it into a positive experience (Grasso et al, 2000).

HYPOTHESIS

The adherence in chronic disease treatment is very low (Sabaté, 2003), being the CPT adherence in CF less than 50 % (Goodfellow et al, 2015). To improve airway clearance in CF patients, there is no therapeutic alternative to CPT, in any case, it has to be combined with physical exercise (Kriemler et al, 2016). Motivation is the best way to optimize treatment adherence (Smith et al, 2010) and the use of carefully selected music during CPT (Grasso et al, 2000) or physical exercise (Calik-Kutukcu et al, 2016) in CF

patients can lead to a positive affective response that could be translated into a improvement in adherence (Smith et al, 2010) and therefore in airway clearance that could maintain the lung function and improve the children's and family member's quality of life.

Baseline hypothesis: Significant differences are expected in chest physiotherapy enjoyment and perception, adherence to daily chest physiotherapy, pulmonary symptomatology and quality of life between participants that use specific composed music as an adjunct to chest physiotherapy routine (intervention group), commercial music as an adjunct to chest physiotherapy routine (control group with music), or no music (control group without music).

OBJECTIVES

Main objective:

To develop a strategy based on music therapy as adjunct to daily chest physiotherapy in children with cystic fibrosis and to evaluate its effects. Instrumental music specifically composed, interpreted and compiled to cystic fibrosis children as an adjunct to chest physiotherapy routine will be used.

Secondary objectives:

• To evaluate the effects of music therapy as an adjunct to chest physiotherapy on enjoyment, perception, adherence to daily chest physiotherapy of patients and family members.

• To evaluate the effects of music therapy as an adjunct to chest physiotherapy on pulmonary symptomatology and quality of life.

METHODOLOGY, TRIAL PLAN AND SCHEDULE

METHODOLOGY

- Study design:

Interventional prospective study on pediatric cystic fibrosis patients. Randomized controlled trial.

- Scope:

Single center: Unit of Pediatric Pulmonology, Malaga Regional Hospital, Malaga, Spain.

- Participants:

Children from the Pediatric Pulmonology Unit at Malaga Regional Hospital who meet all of the following inclusion criteria and none of the exclusion criteria:

- Inclusion criteria:

- Diagnosis of cystic fibrosis based on international criteria (Aldana et al, 2011).
- Children between ages of 2-17.
- Undergoing periodic clinic visits in the cystic fibrosis Unit.
- Understanding the purpose of the study.
- To provide written informed consent.

- Exclusion criteria:

- Children without chest physiotherapy prescription.
- Children with severe hearing loss.
- Children at radiologic or clinical risk of pneumothorax or pneumomediastinum.
- Children with barotrauma in the month prior to entry in the study.
- Children with past history of massive or life-threatening haemoptysis.
- Transplant recipients or children awaiting a lung transplant.

Children / legal guardian must have understood the purpose of the study and express their agreement by signing the informed consent prior to the inclusion in the study (model attached).

- Sample size:

To calculate the sample size, the perception of time taken to complete the routine has been assumed as main variable. According to Grasso et al, (2000) where the control group values in this variable were 0.2±10.2 (mean± SD), considering these values as baseline, a power of 80 %, a confidence level of 95 %, and a similar variability at the end of the study, a difference of 8 minutes would be considered as statistically significant with a sample size of 13 subjects. A total of 39 participants are necessary.

- Randomization:

After providing written informed consent, a random allocation sequence will be carried out using the Epidat program. The participants will be randomly allocated into intervention group, control group without music, or control group with music.

The groups are the followed:

- *Intervention group or TG* (participants that use specific composed music as an adjunct to chest physiotherapy routine).
- *Control group without music or CG* (participants that do not use music as an adjunct to chest physiotherapy routine).
- *Control group with music or PG* (participants that use commercial music as an adjunct to chest physiotherapy routine).

Participants in every group will continue with their usual treatment regimen without modifications.

- Data collection:
Demographic and clinical data will be collected in the case report formulary from each participant (Annex). Specifically: age, gender and respiratory infection exacerbations that requiring hospitalization.

These participants are controlled in the Pediatric Pulmonology Unit at Malaga Regional Hospital, where each child with cystic fibrosis has a detailed clinic history, being the clinical variables systematically included and the treatment updated. Therefore, the present study does not imply additional clinic information collection. Demographic and clinical information will be completed by Pediatricians during the usual follow-up.

In addition, participants will complete a baseline and 2 evaluation questionnaires during the trial-period in order to know children's and family members' chest physiotherapy perception. The questionnaires will be conducted about chest physiotherapy experiences to evaluate the evolution of their perceptions during the trial-period. These questionnaires are designed specifically to know evolution of CPT characteristics such as, enjoyment and perception or time or adherence to daily chest physiotherapy, after the use of music therapy as an adjunct to CPT (Grasso et al, 2000). The perception of pulmonary symptomatology and the impact on the quality of life will be also evaluate using a visual analog scale (VAS) to assess the magnitude of dyspnea in pulmonary diseases such as CF (Bausewein et al, 2007) and the revised cystic fibrosis quality of life questionnaire (Quittner et al, 2000), respectively.

- Study variables:

- *Demographics*:
  - Age (quantitative variable) (unit: years)
  - Gender (qualitative, dichotomous variable) (male / female)

- *Clinics*:
  - Number of respiratory infection exacerbations that requiring hospitalization (quantitative variable)
  - Days of hospitalization per exacerbation (quantitative variable)

- *Chest physiotherapy characteristics*:
  - Use of activities to accompany the routine (qualitative, dichotomous variable) (yes /no)
  - Type of activities used to accompany the routine (toys, stories, music, radio, TV…) (qualitative variable)

- *Chest physiotherapy adherence*:
  - Routine frequency (quantitative variable)

- Number of times per day (quantitative variable)
- Interruptions (qualitative, dichotomous variable) (yes /no)
- Length per session (quantitative variable)

- *Chest physiotherapy attitude:*

  - Response to the routine using a Likert scale (-3 to +3): least enjoyment – neutral - most enjoyment (quantitative variable)
  - Feelings about the routine choosing 3 words to describe these feelings (qualitative variable)

- *Perception of time taken to complete the chest physiotherapy*:

  - Perception of being a long routine (qualitative, dichotomous variable) (yes /no)
  - Time that seems to need the routine (quantitative variable)

- *About the music*:

  - Music use frequency (quantitative variable)
  - Response to the use of music during routine using a Likert scale (-3 to +3): least enjoyment – neutral - most enjoyment (quantitative variable)
  - Usefulness of music during routine (qualitative, dichotomous variable) (yes /no)
  - How music has been useful (qualitative variable)
  - To continue using this music as an adjunct to the routine in the future (qualitative, dichotomous variable) (yes /no)

- *Perception of pulmonary symptomatology and impact on quality of life:*

  - Measurement of the symptoms of dyspnea using a dyspnea visual analog scale (VAS), being 1 no dyspnea and 7 maximal dyspnea.
  - Frequency of respiratory symptoms according to the revised quality of life questionnaire for cystic fibrosis during the previous 2 weeks: cough during the day and night, expectoration and type of expectoration, breathing difficulties, whistling sounds when breathing, and respiratory congestion.

- Development of the instrumental therapeutic music:

An instrumental therapeutic music will be developed specifically to the CF children from the Pediatric Pulmonology Unit at Malaga Regional Hospital to use as an adjunct to each part of the CPT routine according to the CPT strategy of this Unit.

The CPT treatment in this Unit is divided into 3 sections with a total length of about 40 minutes: During the first part, children should be relaxed while the nebulizer inhalation treatment is applied around 10-15 minutes. Next, airway clearance techniques are administered during 20-30 minutes to promote mucus expulsion. Finally, a new relaxation phase of about 5 minutes is proposed, where antibiotic nebulizer treatment is administered if necessary.

The music will be divided into 3 sections related to the 3 parts of the CPT routine:

- Section A: nebulizer treatment
- Section B: CPT work-bronchial clearance
- Section C: relaxation-nebulization

The professional musician will compose, and score-write the different music pieces according to the clinical recommendations from the research group. The composition of about 10 pieces is estimated.

After that, the musician with higher percussion studies will perform the songs with pitched percussion instruments (marimba, vibes, glockenspiel and xylophone) and unpitched percussion instruments (drums, congas, bongos, multi-percussion set and small-percussion instruments).

To record the audio, a portable studio (Tascam) and specific microphones will be used. Subsequently, the audio will be edited with the Cakewalk Sonar Platinum edition software and complied in an audio-CD that will be use by participants in the intervention group.

- Intervention:

After participant recruitment they will complete the baseline questionnaire and be asked to carry out the CPT routine during 6 weeks (Grasso et al, 2000; Canga et al, 2015) as follow:

- *Intervention group or TG*: Using the Music-CD as an adjunct to each part of the CPT routine. The Music-CD will be provided after baseline questionnaire.
- *Control group without music or CG*: Continuing with the usual CPT without modifications.
- *Control group with music or PG:* Using commercial music as an adjunct to each part of the CPT routine.

As has been comment, the CPT treatment in this Unit is divided into 3 sections with a total length of about 40 minutes: During the first part, children should be relaxed while the nebulizer inhalation treatment is applied around 10-15 minutes. Next, airway clearance techniques are administered during 20-30 minutes to promote mucus expulsion. Finally, a new relaxation phase of about 5 minutes is proposed, where antibiotic nebulizer treatment is administered if necessary.

Participants in every group will continue with their usual treatment regimen without modifications. Follow-up changes or treatments modifications are not planned in any case.

A second questionnaire will be completed after 6 weeks and participants will continue managing the CPT routine in the same way during a new 6-week period. After that, the final questionnaire will be completed (Grasso et al, 2000) and the music-CD will be offered to CG and PG participants.

- Statistical analysis:
Statistical analysis will be performed using SPSS Software.

Initially a descriptive analysis of the study variables will be carried out, the values of the continuous variables will be summarized in a table where their corresponding means and standard deviation will be shown. The categorical variables will be presented in absolute and relative frequencies.

To compare qualitative measures Chi-square or Fisher tests will be used, and ANOVA or Kruskal-Wallis tests to quantitative.

To contrast the differences in the evolution of the variables between the different groups the multivariate analysis of variance test of repeated measures (MANOVA) will be applied with a factor between subjects (group) and a factor intra subjects (different moments of the intervention). Depending on the compliance of the sphericity condition, the Greenhouse-Geisser correction will be used. To contrast the differences between baseline and final measures in each group Wilcoxon test will be applied. To compare response to using music after the intervention into TG and PG, Mann–Whitney U test was used.

To compare response to using music after the intervention into TG and PG, Mann–Whitney U test will be used.

A significance of 5% ($p<0.05$) will be required to consider a difference as statistically significant.

- Limitations:
Selection bias, people who decline to participate in the study can introduce a selection bias, this can be controlled in the data analysis phase, analyzing if there are differences between people who participate and people who do not.

TRIAL PLAN

The research group will meet to define the instrumental music that will be composed to CF children as an adjunct to each part of CPT routine. After that, the musician member of the research group will compose and score-write the musical pieces. Then, he will interpret these songs playing percussion instruments and record the pieces.

The research group will supervise and select the adequate songs to each part of CPT and then, the musician will edit the musical pieces selected according to the clinical recommendations from the Pulmonology Unit and the Physiotherapist specialist in children CPT.

The music chosen will be compiled in an audio-CD and, after that moment, the recruitment and the intervention will be started and carried out as described above.

Demographic and clinical data will be collected and the questionnaires fill in as mentioned before.

Finally trial data will be analyzed systematically and diffused.

SCHEDULE

Tasks	Year 1												Year 2											
Months	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Initial meeting and definition of the music to be developed																								
Music composition/ Music scores-writing																								
Interpretation/Recording of musical pieces																								
Musical pieces supervising and selection																								
Edition of the musical pieces selected																								
Study analysis																								
Music-CD compilation																								
Recruitment																								
Demographic and clinical data collection																								
Filled in questionnaires																								
Statistical analysis																								

ETHICAL CONSIDERATIONS

The interventions associated with each group are not related with the use of investigational drugs or devices. The aim of this trial is to compare the usual CPT routine prescribed in CF patients with the use of commercial music or an instrumental music specifically composed, interpreted and compiled to CF children as an adjunct to each part of CPT routine without modifying the usual treatment regimens or programmed clinic visits. This music therapy intervention could help to establish CPT as a positive routine that could improve its adherence and, therefore, the airway clearance. It could maintain the lung function and improve the children's and family member's quality of life.

The safety profile in each group of study: intervention group (music-CD as an adjunct to chest physiotherapy routine), control group without music (usual chest physiotherapy routine) and control group with music (commercial music as an adjunct to chest physiotherapy routine) is favorable, being optimum the benefit / risk balance.

At the end of the trial period, the music-CD will be offered to both control groups (CG and PG participants).

On the other hand, this music therapy intervention does not presents risks for CF participants due to the intervention consists of using the music as an adjunct to usual CPT.

The study will be conducted according to the Declaration of Helsinki and the Spanish and regional protocols concerning to ethics in human research.

The data confidentiality is assured according to the Spanish protection of personal data 15/1999 Law and the basic law 41/2002 that regulates patient autonomy and rights and obligations in terms of information and clinical documentation.

All the researchers involved in the project are committed to preserve the confidentiality of the information provided by participants.

The study has been applied to the Ethics in Human Research Committee of Malaga Regional Hospital "CEI Provincial de Málaga" to be approved.

Participants (children / legal guardian) must have known and understood the purpose of the study and express their agreement by signing the informed consent prior to the inclusion in the study (model attached). The participation is voluntary.

APPLICABILITY

The music therapy strategy proposed in this project has a direct applicability in healthcare practice due to it is expected an improvement in chest physiotherapy enjoyment and perception, adherence to daily chest physiotherapy, pulmonary symptomatology and quality of life between participants that use specific composed music as an adjunct to chest physiotherapy routine without modifying their treatments and follow-up. These will lead to a reduction in the burden of the disease, which can be translated into improvements in Healthcare systems.

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ANNEX - CASE REPORT FORMULARY

Age:

Gender:

Respiratory infection exacerbations that requiring hospitalization:

	Pre-study period	Study-period
Number of exacerbations		
Days hospitalized per exacerbation		

QUESTIONNAIRES:

 Chest physiotherapy characteristics:

- Use of activities to accompany the routine (yes /no)
- Type of activities used to accompany the routine (toys, stories, music, radio, TV…)

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□ Chest physiotherapy adherence:

- Routine frequency
- Number of times per day
- Interruptions (yes /no)
- Length per session

□ Chest physiotherapy attitude:

- Response to the routine using a Likert scale (-3 to +3): least enjoyment – neutral - most enjoyment
- Feelings about the routine choosing 3 words to describe these feelings

□ Perception of time taken to complete the chest physiotherapy:

- Perception of being a long routine (yes /no)
- Time that seems to need the routine

□ About the music:

- Music use frequency
- Response to the use of music during routine using a Likert scale (-3 to +3): least enjoyment – neutral - most enjoyment
- Usefulness of music during routine (yes /no)
- How music has been useful
- To continue using this music as an adjunct to the routine in the future (yes /no)

□ Perception of pulmonary symptomatology and impact on quality of life:

- Measurement of the symptoms of dyspnea using a dyspnea visual analog scale (VAS), being 1 no dyspnea and 7 maximal dyspnea □

- Frequency of respiratory symptoms according to the revised quality of life questionnaire for cystic fibrosis during the previous 2 weeks:

always, often, sometimes, never

Coughing during the day..... □ □ □ □
Wake up at night because of coughing..... □ □ □ □
To expectorate (spit out the mucus)..... □ □ □ □
Mucus appearance: □ Watery □ Yellow/Transparent □ Yellow-Green □ Green/Bloody □ I do not know
Respiratory congestion..... □ □ □ □
Whistling sounds when breathing..... □ □ □ □
Breathing difficulties..... □ □ □ □