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STUDY PROTOCOL

Respiratory Muscle Training in Hemodialysis Patients-A Clinical Trial Protocol

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Abstract

Introduction: Hemodialysis patients with chronic kidney disease present a complex syndrome with many effects on cardiovascular, respiratory and musculoskeletal systems. With regard to musculoskeletal structure, there is a progressive loss of mass with consequent increase of muscle weakness, limited resistance, exercise intolerance and fatigue, as well as functional and morphological abnormalities, typical of uremic myopathy. Respiratory muscles are also affected, and the rehabilitation may help patient's performance in terms of strength and respiratory resistance with programs developed at the intradialytic time.

Objective: Analyze the impact of inspiratory muscle training (IMT) on muscle strength, functional capability and quality of life of hemodialysis patients with chronic kidney disease.

Methods: Controlled and randomized clinical trial with inclusion of patients who are treated by dialysis unit from a university hospital. It will be included patients older than 18 years, both sexes, who underwent hemodialysis for more than six months and who assigned an informed consent form. The patients will be allocated into two groups: IMT group, which will be carried out with power breathe, and control group. Everyone will be evaluated according to demographic data, respiratory muscle strength, functional and lung capability and quality of life. Another evaluation will be performed three months after the first one.

Keywords: Renal Dialysis; Respiratory Exercises; Respiratory Muscles; Spirometry; Quality of Life; Walking Test

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem, affecting 10 to 12% of the population, with increase of incidence and prevalence [1,2]. These patients may develop with muscle strength loss, weakness, limited resistance, exercise intolerance and fatigue, as well as morphological and functional abnormalities, typical of uremic myopathy [3-6].

The evolution of the disease and the morphofunctional alterations are not clarified, but there are some factors that may contribute to its development, such as release of uremic toxins, anemia, alteration of energetic metabolism, decrease of muscle blood flow and peripheral neuropathy [7]. The respiratory system also suffers with changes, ventilatory muscles are affected and there are reports about low cardiorespiratory conditioning and limitation of life's activities [8].

Moreover, patients undergoing hemodialysis (HD) are affected by body fluid overload during the interdialytic period, with increase of pulmonary capillary pressure and, consequently, pulmonary edema and pleural effusion. These changes may impair gas exchange, pulmonary function and functional capacity of patients [5].

The need of HD three times a week, metabolic disturbances and psychosocial impact caused by dialysis dependence determine a greater impairment. Therefore, several studies are looking for protocols that minimize the progression of functional disability and that can be performed at interdialytic time [9-11].

Dyspnea arises in these patients and is often undervalued, but it is a self-limiting symptom [11], which can be handled with Inspiratory Muscle Training (IMT). Nowadays, this alternative regarding to traditional rehabilitation programs has been highlighted by improving the performance of respiratory muscles. The IMT shows positive results in the approaching of the Chronic Obstructive Pulmonary Disease (COPD), Heart Failure (HF) and in CKD, with a positive response in strength, functional capacity and reduction of dyspnea [12-15].

Despite of the benefits, we did not find in the literature a gold standard for prescription of IMT during HD in patients with CKD [14-18] or the follow-up of patients who underwent IMT to analyze the duration of training effects. Therefore, it is necessary to select a protocol and a follow-up of these patients to observe the maintenance of training effects.

Objective and Hypothesis

Analyze the impact and the maintenance of IMT effects on muscle strength, functional capacity and quality of life of patients with CKD in HD. The formulated hypothesis is that the inspiratory training will increase respiratory muscle strength with a positive impact on the functional capacity and quality of life of these patients.

Methods

Study Design

A controlled and randomized clinical trial that involve patients with CKD undergoing hemodialysis treatment by the HD sector at a university hospital in são paulo city, brazil.

Participants

Patients will be selected according to the following inclusion and exclusion criteria: **(A) Inclusion:** patients with CKD who underwent hemodialysis for more than six months, both sexes, older than 18 years, who are clinically stable and signed the informed consent form approved by the hospital's ethics committee. **(B) Exclusion:** patients with prior or current myoarticular or neurological disease who require some urgent or elective surgical intervention during protocol, systolic blood pressure (sbp) ≥200mmhg or ≤60mmhg, diastolic blood pressure (dbp) ≥120mmhg or ≤40mmhg, decompensated diabetes mellitus and acute systemic infection.

Variables

Primary Outcomes: Increase in inspiratory muscle strength and improvement in functional capacity assessed by the increase in covered distance in the six-minute walking test.

Secondary outcomes: improvement in inspiratory muscle strength observed in three months after the end of the protocol.

Ethical Considerations: This protocol was approved by the institution's ethics and research committee and will be recruited with case 64024117.4.0000.5479 and registered in clinical trials NCT no. Nct03153124

Hemodialysis

All patients will be treated with HD support for more than six months. The sessions are held three times a week, with an average duration of four hours. The HD is made with Polysulfone Membrane (Fresenius®), Sodium Bicarbonate (138.0meq/L), Potassium (2.0meq/L), Calcium (2.5meq/L), Magnesium (1.0meq/L), Chloride (108.5meq/L), Acetate (3.0meq/L) and Bicarbonate (32.0meq/L). The place to perform the HD has temperature and humidity control, as well as adequate lighting.

Study Protocol

All participants will be evaluated and re-evaluated by a single expert and skilled examiner to perform all procedures, who will not be informed about the aims of the study (Figure 1) [19]. A Standard Form will be used to collect data such as age (years), gender, personal history, medications in use, time of HD (months) and etiology of the disease.

All patients will undergo evaluation and re-evaluation in the pre-hemodialysis period in the second session of the week, with a maximum interdialytic period of 48 hours being respected. In this session, it will be measured ventilatory muscle strength, spirometer, functional capacity and quality of life.

Ventilatory Muscle Strength

Measurement will be performed by digital manovacuometer (kh2 power breathes international ltd. Warwickshire, England). The patients will be sitting with a trunk at an angle of 90o in relation to the thighs and airway occluded by the nose clamp. The values

obtained will be the pimax, a measure that predicts the static inspiratory muscle strength. The patient will be instructed to perform a deep expiration until functional residual capacity, and then he/she will inspire with the greatest strength that can achieve. A rest interval of one minute will be respected between measures that will total three, being observed difference values less than 10% among them [14]. In this same apparatus, it will be collected variables of peak inspiratory flow, volume and s-index.

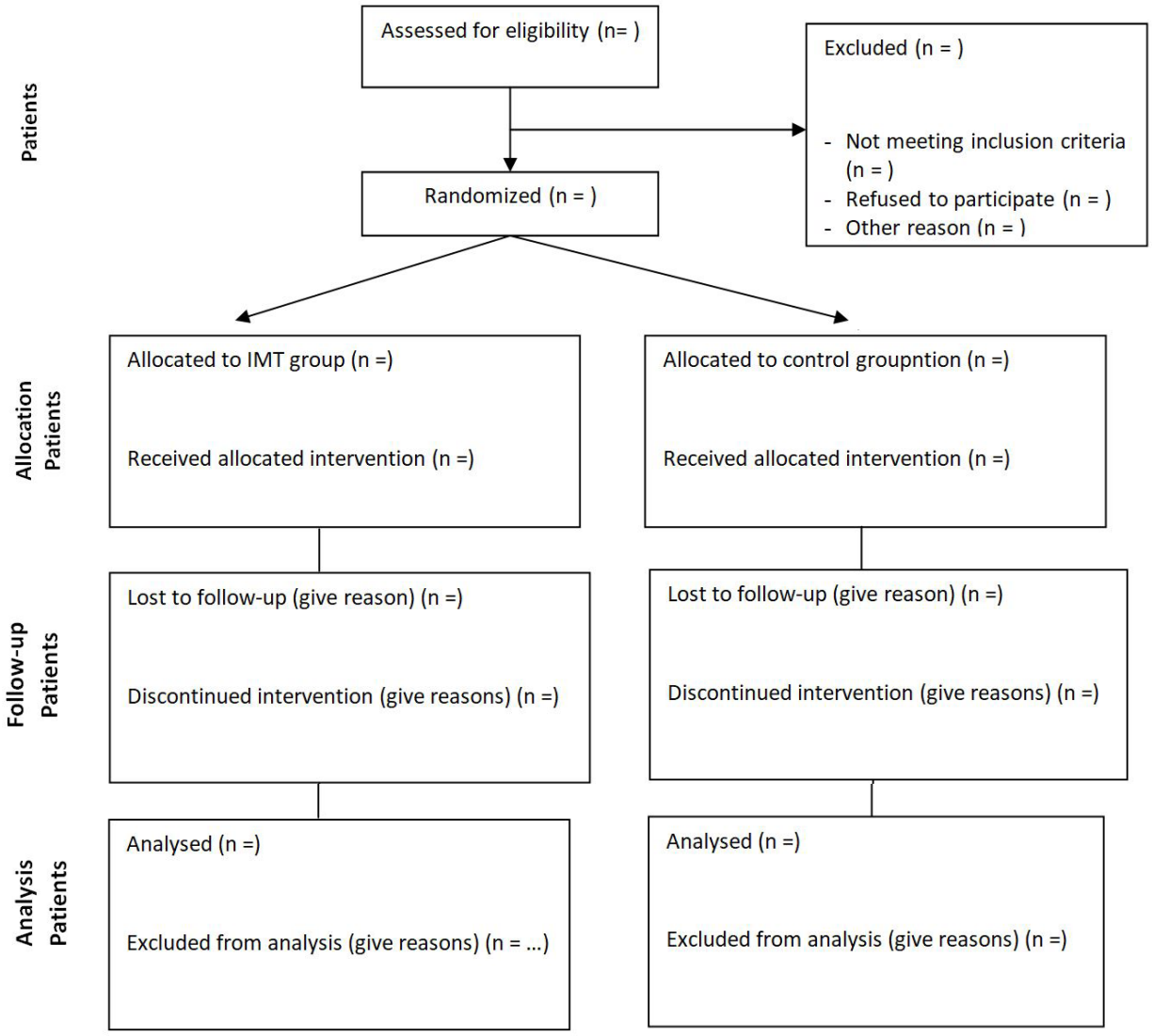

Figure 1: Modified Consort Flow Diagram for Individual Randomized Controlled Trials of Nonpharmacologic Treatments (Consort, 2017) [19]

To determine predictive values of each patient, according to age and sex, we will use the equations of neder, *et al.* (1999) 20: MIP in men: y = -0.80 (age) + 155.3, EPE = 17.3; MIP in women: y = -0.49 (age) + 110.4, EPE = 9.1; mw in men: y = -0.81 (age) + 165.3, EPE = 15.6; PEMAX for women: y = -0.61 (age) + 115.6, EPE = 11.2.

Six-Minute Walking Test

it will be conducted under the american thoracic society guidelines [21] in a 30-meter runner. In the beginning of the walking, it will be evaluated: blood pressure (bp, mmhg) measured with a sphygmomanometer (tycos®), heart rate (hr, bpm), respiratory rate (f, Ipm) observed for one minute with the aid of a stopwatch, peripheral saturation of oxygen (SpO2, %) with nonin® oximeter and graduation of the perception of effort with borg scale. At the end of the walking, the distance traveled will be measured and monitoring once more the hr, f, SpO2 and borg scale. The examination will be performed under the guidance and control of the same physiotherapist, who will not accompany the patient during the walking.

Spirometry

It will be applied by koko spirometer apparatus (koko spirometer from pds instrumentation®). The values will be predicted by age, height (m) and sex according to the equation of Pereira, et al. [22]. The patient will remain sitting throughout the test using a nasal clamp and he/she will be instructed to perform a maximal inspiration followed by a rapid and sustained expiration for at least six seconds or until the physiotherapist discontinues the procedure. The patient will also receive verbal stimulation

to perform all stages [23]. Forced vital capacity (fvc, l), forced expiratory volume in the first second (fev1, l) and relationship between them (fev1 / fvc) will be evaluated.

Quality of life questionnaire

kidney disease and quality of life timshort form (kdqol-sftm) will be used for renal patients, which was translated and validated in Brazil by Duarte, *et al.* [24]. The patient will be instructed to answer the questionnaire alone [25].

Albumin, PCR and KT/V

The results of the creative protein, KT/V and albumin tests will be collected on the day of evaluation and re-evaluation. All these exams are collected as part of the routine of these patients, and then no new collections are necessary for the research.

Randomization and Allocation

Patients will be randomized into two groups according to random.org/sequences in Inspiratory Muscle Training (IMT) or control group.

Control Group

After evaluation, the patient will be followed-up by routine care, such as a routine collection of urea, creatinine, potassium and venous blood gases, once a month, before and after hemodialysis, blood culture collection for those who undergoing hemodialysis through Catheter (Shilley or permcath long-stay catheter). They will also receive guidance from the service, about their illness, their fistula care and the importance of practicing physical activity, healthy eating, water intake, cessation of smoking and personal care.

IMT Group

In addition to usual care, patients will undergo IMT within the first two hours of the HD session. The IMT protocol will be performed with the power breathe international ltd linear loader (warwickshire, England), with a load of 30 to 40% of the maximal inspiratory pressure (MIP) value For A period of three months. The load oscillation is for absolute value calculation and proper adjustment of the apparatus. The sessions will occur three times a week for 30 minutes/day [26] under the supervision of a physiotherapist who will not know the study aims.

In the first week, for adaptation to the device, the patients will perform the training with no load. They will be advised to remain sitting and with nasal clamp throughout the protocol. Every ten minutes, they will be informed of the elapsed time and questioned about possible symptoms. The variables pa, fc and SpO2 will be measured in the beginning and in the end of each session. At the end of each week, patients will be re-evaluated for MIP, so that the load values will be increased if it is necessary. Each patient will have his/her logbook to record all MIP values during the three months, as well as the exact percentage of the load adjusted every week. After three months of termination of the protocol, a new MIP evaluation will be performed.

Session Interruption Criteria

The session will be interrupted if the patient presents sbp ≥ 200mmhg or ≤60mmhg, dbp ≥ 120mmhg or ≤40mmhg, precordial pain, dyspnea, nausea, vomiting, pallor, sweating or cold extremities.

Statistical Analysis

For the sample calculation, t-student test was used to compare the means between the groups for the outcome of distance travelled in the six-minute walk test. We adopted a Significance Level of 5% and test power of 80%. We used 70 meters as mean difference between groups based on the control group of a parallel study, which resulted in a sample of 23 patients for the control group and 23 patients for the respiratory muscle training group.

For statistical analysis data set will be used the program SPSS 13.1. The level of significance will be 0.05. To analyze continuous variables will be used the t-student test, chi-square test for nominal data and mann-whitney for ordinal data.

Discussion

This paper provides a detailed description of a randomized clinical trial to determine the impact of the IMT protocol on functional capacity, respiratory muscle strength and quality of life in patients with CKD undergoing HD.

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