Acute and Chronic Effects of Exercise in Health

Effects of an intradialytic cardiovascular rehabilitation program on functional capacity and cardiac function: ICRP trial

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Abstract - Introduction: Chronic kidney disease (CKD) is a worldwide public health problem associated with an increased risk of death from cardiovascular complications. Although previous studies have described significant improvements in exercise in functional capacity and quality of life in patients with end-stage kidney disease (ESKD), there is a lack of studies that propose to assess its impact on cardiac function using transthoracic echocardiogram (ECHO). In addition, most of the intradialytic exercise protocols are inconsistent, and incomplete regarding their intensity prescription, time of intervention, and monitoring. **Methods:** The present study aims to evaluate the effects of an intradialytic cardiovascular rehabilitation protocol (ICRP) using medium intensity aerobic exercises, for 30 min. on cardiac function and functional capacity. In this 6-month longitudinal study, heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, peripheral oxygen saturation (SpO2) and modified Borg scale will be analyzed in all HD sessions. The cardiac function will be evaluated by left ventricular ejection fraction (LVEF) through ECHO; functional capacity by the six-minute walk test (6MWT); quality of life through the SF-36 questionnaire and routine laboratory tests and KT/Vsp calculation before and after the ICRP. **Conclusion:** ICRP protocol will be examined and is expected to improve cardiac function, functional capacity, and quality of life in ESKD patients on hemodialysis.

Keywords: exercise, intradialytic, chronic renal failure, dialysis, quality of life, functional capacity, cardiac function.

Introduction

In patients with ESKD, dialysis treatment directly contributes to sedentary behavior that can further worsen the cardiovascular health status of these patients and, consequently, a high mortality rate[1,2]. In addition, patients on dialysis have reduced functional capacity assessed through maximal oxygen consumption (VO2 max.), impaired physical performance tests (walking, squatting, climbing, and sitting and standing tests), decreased physical activity, muscle mass, and strength[3]. Among the mechanisms involved in the functional disability observed in this population, oxidative stress and the consequent mitochondrial dysfunction, insulin resistance, impaired lipid metabolism, and active proteolytic pathways, all promote muscle atrophy[3]. These disorders are directly related to renal failure and comorbidities, as well as occasional adverse effects of dialysis that induce marked metabolic changes caused by increased ultrafiltration (hypovolemia, rapid changes in electrolyte concentrations) and systemic inflammation[2].

However, higher levels of physical function are related to lower morbidity and hospitalization rates and better quality of life in patients on renal replacement therapy[4]. There is also evidence that short-term (2-6 months) moderate-intensity supervised aerobic exercise programs induce improvement in cardiorespiratory function. In this context, there are reports that intradialytic exercise is superior to the interdialytic model[5,6]. The reason may be the better adherence of patients who feel safer when exercising under the supervision of specialized professionals and the greater removal of uremic toxins due to the increase in blood flow generated by muscle contraction[3,6]. However, despite all the benefits mentioned, exercise prescription for patients with ESRD is less common than for other chronic diseases[6]. In addition, clinical trials that address clinical outcomes after controlled physical activity for patients with ESRD have

as their main limitations the wide variety of protocols reported and the insufficient or incomplete application of exercise prescription[4].

Therefore, the present study aims to demonstrate a safe intradialytic cardiovascular rehabilitation program and its impact on functional capacity, cardiac function, and quality of life of patients with end-stage renal failure on regular hemodialysis.

Methods

Trial design

This is a longitudinal, non-randomized study involving patients in regular hemodialysis treatment. Recruitment of the research subjects will start in 2022, duly approved by the Ethics Committee of the Clementino Fraga Filho University Hospital under the number 180/10 and registered in the Brazilian Registry of Clinical Trials (REBEC) platform identified by UTN: U1111-1204-212. The conduction of this randomized clinical trial will be released according to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) and the conception of this study was based on the guidelines of the standard protocol items: recommendations for interventional trials (SPIRIT).

Study population

CKD patients' stage 5D, above 18 years of age, in HD with an arteriovenous fistula, 4 h per session, 3 times a week for at least 3 months, will be included in this study. Patients with severe heart failure; severe lung disease, uncontrolled diabetes, anemia with hemoglobin below 8 g/dL neurological problems; category Active/ Very Active in the International Physical Activity Questionnaire[7]; musculoskeletal disabilities, and any others that prevent the use of the cycle ergometer will be excluded.

Study design

The study has three phases lasting 32 weeks. All subjects will be submitted to transthoracic echocardiography, evaluation of functional capacity by six-minute walk test (6MWT)[8], and quality of life by instrument Summary Form of Quality of Life in Kidney Disease - KDQOL-SF[9]. Laboratory data will be collected from medical records during the period of the survey. The three phases are described in Figure 1.

Phase I: Consists of an 8 weeks control period between −8W and 0W. In this pre-intervention phase, patients will undergo regular dialysis and routine laboratory tests, echocardiography, KDQOL-SF and 6MWT will be performed.

Phase II: Total duration of 16 weeks, with ICRP in all HD sessions (three times a week) represented by the

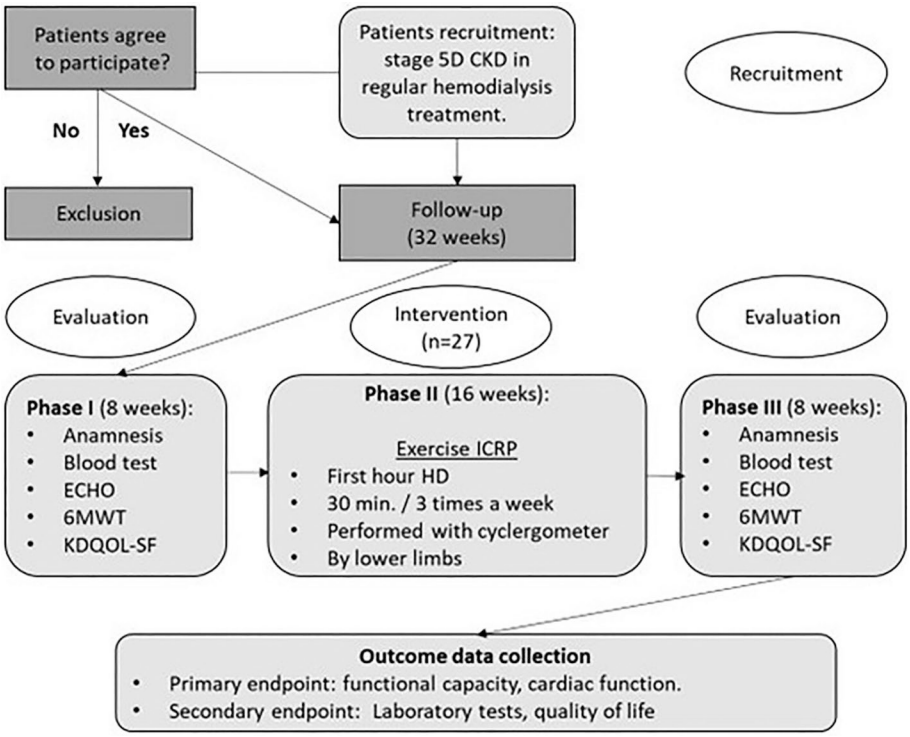

Figure 1 - Study design. CKD: chronic kidney disease; ECHO: transthoracic echocardiogram; 6MWT: six-minute walk test; KDQOL-SF: Summary Form of Quality of Life in Kidney Disease; ICRP: intradialytic cardiovascular rehabilitation program; HD: hemodialysis

period 0W to 16W. During the procedure, systolic (SBP) and diastolic (DBP) blood pressure, heart rate (HR), and peripheral oxygen saturation (SpO2) were measured by the portable oximeter (Octivetech 300C, clinical guard, Atlanta, USA) will be monitored. Borg scale[10] in 4 moments (0, 10, 20 and 30 min). At 16W, 6MWT will be realized.

Phase III: Total of 8 weeks, post-ICRP between 16 week and 24 week. Patients will undergo regular dialysis and routine laboratory tests, ECO, and KDQOL-SF. On 24 week, the 6MWT will be held.

Sample size

As a basis for estimating the sample size, the results of the pilot study that observed improvement in cardiac function through a two-dimensional transthoracic echocardiogram (left ventricular ejection fraction) with an intradialytic exercise protocol lasting 4 months were used.

For the difference in cardiac function through analysis of left ventricular ejection fraction of 8% with a standard deviation of 10.1% assuming $\alpha = 0.05$ and desired power = 0.8, a total of 27 patients will be included.

Intervention

Prescription protocol for intradialytic exercise

Among the patients eligible for the study, cardiovascular risk stratification will be performed[11] for better supervision and safety during exercise. The adequacy of the protocol execution will also be done during the ideal HD period, avoiding exercises in the first and last hour of dialysis due to possible negative effects (hypervolemia, nausea, and cramps) and adverse events.

According to the recommendations of the international guidelines for cardiovascular rehabilitation[11,12], patients will undergo aerobic exercises in the lower limbs for 30 min from the first hour of hemodialysis on a cycle ergometer (model: Original Pedlar/Battle Creek). The intensity of exercise dosimetry will be determined by a formula for calculating heart rate reserve (HRR)[12] and maximum HR[12] at moderate intensity (40-84% of HRR)[11] maintaining the BORG subjective effort scale between 13-15. Initially, for patients with low exercise tolerance, a period of familiarization with the exercise protocol will be performed. Blood pressure will be monitored before exercise, every 10 min of conditioning, and after the end of the activity. HR will be monitored continuously using a frequency meter (Polar F1, Polar Electro Oy, Kempele, Finland). According to the established criteria, the protocol will be interrupted in case of an increase in SBP above 170 mmHg or a persistent drop of more than 10 mmHg; an increase of more than 20 mmHg in DBP; dizziness; pallor; cyanosis; lipothymia, presyncope; dyspnea disproportionate to the intensity of effort; clinical manifestation of chest discomfort; signs suggestive of left ventricular failure, such as crackling rales on pulmonary auscultation. Before each training, an evaluation will be carried out. Patients who have changed blood pressure (SBP > 180 mmHg and/or DBP >110 mmHg), postprandial blood glucose < 90 mg/dL, gain in interdialytic weight greater than 5 kg and any significant complaints will be prevented from exercising on that day or for as long as such changes persist. The protocol is described in Figure 2.

Study endpoints

Primary endpoint

The primary endpoint of this study will be presented:

Functional Capacity: 6MWT will be performed according to recommendations of the American Thoracic Society recommendations[8]. Patients will be instructed to walk as far as possible at the maximum possible speed for 6 min. The walkway should be 30 m long. An evaluator will provide standardized encouragement every minute. The patient will be allowed to rest during the test, if necessary, and this time will be included in the total test time. The test will be performed twice with an interval of 1 h between them. The best distance will be considered. Normal predicted values of 6MWT distance will be calculated using the equations proposed by Britto et al[13].

Cardiac function: Transthoracic two-dimensional echocardiography (Acuson X300 / Siemens model) will be performed in phases I and III, pre and post-intervention of the ICRP protocol, by the same cardiologist in the Cardiology sector. We will only evaluate the main cardiac morpho-functional aspects pertinent to the study (normal values with percentiles 5 and 95): diastolic diameter measurements (40.3-54.3 mm) and left ventricular systolic diameter (23.8-33.4 mm), the thickness of the left ventricular posterior wall (7.0-9.3 mm) and left ventricular ejection fraction (65.6-76%).

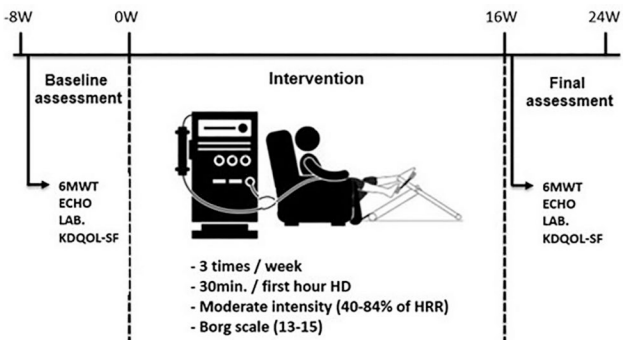

Figure 2 - Prescription protocol for intradialytic exercise. ECHO: transthoracic echocardiogram; LAB.: laboratory tests; 6MWT: six-minute walk test; KDQOL-SF: Summary Form of Quality of Life in Kidney Disease; HRR: heart rate reserve

Secondary endpoints

The secondary endpoints will be demonstrated through the following analyzes: Laboratory tests and KT / Vsp calculation: Patients' medical records will be evaluated for hemoglobin (g/dL), potassium (mg / dL), sodium (mg / dL), phosphorus (mg/dL) and PCR. The KT/Vsp was calculated by the Daugirdas formula: KT / Vsp = 2.2-3.3 * (R-0,003-VUf / Weight) 21, where K = dialysis coefficient of urea; T = dialysis duration in minutes; V = volume of distribution of urea in ml; R = rate of reduction of urea (urea-post-urea-pre); VUf = volume of ultrafiltration of the dialysis session in mL and Weight in kg.

Quality of life: For the evaluation of QOL will be used the Kidney Disease Quality of Life Summary Form - KDQOL-SF[9]. The interview for the application of the questionnaire will be carried out by the same evaluator in 0 week and 24 week. The KDQOL-SF is a self-administered specific instrument for the assessment of end-stage renal disease, which has 80 items[9]. KDQOL includes the Short-Form Health Survey Item (SF-36) and adds 11 dimensions specifically targeted to kidney disease, which are: symptoms, effects of kidney disease on daily life, problems caused by the disease, work status, cognitive function, social interaction, sexual function, and sleep. It also includes three additional scales: social support, encouragement from the dialysis team, and patient satisfaction[9].

Statistical considerations

For descriptive analysis, the results will be presented as mean ± standard deviation or median (interquartile range), according to the symmetrical or asymmetrical distribution of the variables, respectively. The values obtained will be analyzed using the Student's t-test (paired) for quantitative variables of parametric distribution and the Wilcoxon test for non-parametric distribution data. Such tests will be used to compare before and after the intervention. Differences will be considered significant when $p < 0.05$ (two-tailed test).

Discussion

CKD patients have skeletal muscle dysfunction due to low-grade chronic inflammation and oxidative stress[3], because of reduced renal function. Mitochondrial dysfunction is a key mechanism for activating proteolytic pathways that promote muscle atrophy[14]. Recent studies show an association between physical disability and high rates of hospitalization, cardiovascular complications, and mortality in individuals with CKD[3].

Physical training studies in patients with CKD confirm substantial improvements in leg muscle size[13] and the potency corresponding to morphological changes in muscle capillary density, improvements in oxidative metabolism, muscle mitochondrial biogenesis, and attenuation of systemic inflammation[3,14]. As a consequence of these adaptive mechanisms generated by exercise, several studies have described significant improvements in functional capacity and quality of life in ESKD patients through intradialytic aerobic exercise programs, but have extremely varied intensity and intervention time, which makes its application in clinical practice difficult[3]. However, that does not mention the prescription of intradialytic exercise used in their methods[6].

To date, very few studies have evaluated cardiac function using two-dimensional transthoracic echocardiography[15]. Despite this scarcity, some researchers have demonstrated significant improvement in cardiac function assessed by echocardiography, evidenced by increased ejection fraction through intradialytic aerobic exercises for 3 months, for 30 min with moderate intensity (target heart rate between 60 to 70% of HR maximum)[15]. Nevertheless, this benefit is not fully elucidated in the literature.

In this study, we hypothesize that a clear intradialytic exercise prescription can promote clinically significant improvements in functional capacity, cardiac function, and quality of life using the supervised aerobic intervention of moderate intensity for three months. We hope to describe effective treatment strategies for ESKD patients on hemodialysis.

Trial status

This study will start in 2021. Recruitment is expected to be completed by the end of 2022 and we believe that the trial will be completed, and results will be available in 2023.

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