Supervised exercise protocol for lower limbs in subjects with chronic venous disease: an evaluator-blinded randomized clinical trial

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Study protocol

Abstract

Background : Chronic venous insufficiency (CVI) causes pathophysiological changes in lower limb muscles, particularly calf muscles, and limits ankle range of motion (ROM). These changes reduce functional activities and decrease quality of life (QOL). Although several studies have shown benefits of exercise (strengthening the calf muscles to improve calf muscle pumping and QOL) in patients with CVI, few studies are randomized controlled trials. This has led to a weak indication of exercise for the treatment of patients with CVI. The aim of this study is to analyze the effects of a supervised exercise program to improve calf muscle endurance as well as QOL in patients with CVI.

Methods: This is an evaluator-blind, randomized clinical trial with an 8-week duration and a follow-up evaluation at week 16. A pilot study with subjects with CVI diagnosis will be performed to calculate sample size. The participants will be randomly allocated (1:1) into a treatment or control group (usual care/no intervention). The treatment intervention consists of a bi-weekly supervised exercise program of the lower limbs that will include aerobic training, strengthening, and cardiovascular exercises. The participants from both groups will participate in a health education lecture. Primary outcomes are changes in calf muscle endurance and QOL score. Secondary outcomes are changes in exercise capacity, ankle ROM, electrical muscle activity and cardiac output. First statistical comparison will be performed after 8 weeks intervention.

Discussion : Patients with CVI may have an impaired calf muscle pump and decreased exercise capacity. A randomized controlled trial evaluating a supervised exercise program will provide much needed information on the management of CVI to promote health and independence.

Background

Chronic venous insufficiency (CVI) is a common health problem and may cause significant morbidity and mortality [1]. It develops when venous pressure is increased and blood return is impaired. Several mechanisms may result in blood flow impairment including incompetent valves (superficial or deep veins), perforating veins, venous obstruction or a combination of these mechanisms. This leads to general or local venous hypertension, mainly while standing or ambulating, contributing to macro or microcirculatory hemodynamic impairments [2] and local tissue ischemia [3]. CVI includes a wide range of clinical signs varying from varicose veins and uncomplicated telangiectasia to venous ulcerations [1,4].

Patients with CVI may develop musculoskeletal changes, mainly in the calf muscle such as muscle fiber atrophy [5], leading to abnormal cadence [6], reductions in muscle strength and function [7]. A decrease in the skeletal muscle pump worsens venous hypertension, leading to excessive accumulation of fluid and fibrinogen in subcutaneous tissue, which in turn causes edema and/or lipodermatosclerosis, and may lead to venous ulcers [2,8,9]. Additionally, ankle joint movement is decreased [10] and is associated with a

higher risk of venous ulcers. Conversely, satisfactory ankle dorsiflexion and effective function of the calf muscle pump prevents edema and venous ulcers [11].

Effective calf muscle pumping, even in the presence of valve dysfunction or venous obstruction, may develop a compensation mechanism (assisting in venous return) and thereby decrease CVI symptoms. Some studies have shown the benefits of exercise therapy in participants with CVI with an emphasis on strengthening the calf muscle for improved calf muscle pumping [12-14]. An improvement in the hemodynamic function of calf muscle pumping (represented by the ejection fraction and residual volume fraction) was described after a supervised lower limb strengthening and stretching exercise program [13], and after 8 consecutive days of isometric strengthening and resistance exercises in the calf muscle [15] for participants with CVI. Other authors [16,17] have highlighted the importance of progressive resistance exercises and supervised aerobic training to promote ulcer healing and improve cutaneous microvascular reactivity in participants with CVI.

A systematic review [18] focusing on physical exercise for the treatment of CVI without ulcers found only two studies that met the eligibility criteria. Although both concluded that physical exercise led to an increase in venous filling time and ejection fraction, indicating an improvement in venous hemodynamics, the evidence quality was considered very low with a high risk of bias. Considering that resistance training and progressive isometric exercises are routinely prescribed for other cardiovascular diseases (such as peripheral obstructive arterial disease and coronary artery disease) [17] and that evidence-based exercise programs tested in CVI participants remain limited, we aim to assess the efficacy of a supervised exercise program to improve calf muscle endurance and QOL as well as to asses ankle range of motion, electrical muscle activity, exercise capacity and cardiac output in participants with CVI. Additionally, we aim to determine if the possible gains achieved in a supervised training program remain after an unsupervised period.

Hypotheses

We hypothesize that a supervised lower limb muscle-training program in participants with CVI will improve calf muscle endurance and QOL scores.

Methods And Analysis

This is an evaluator-blinded, randomized controlled superiority trial with 2 parallel groups, and a 1:1 allocation ratio, with a 8-week intervention period and outcomes measured at baseline, 8 weeks and 16 weeks as a follow-up evaluation. First statistical comparison will be performed after 8 weeks of intervention.

Trial Design

The evaluations will start in January 2020. After evaluation, participants will be randomly allocated to 2 evaluator-blinded groups: treatment group (TG) and control group (CG). The randomization.com program

will be used to randomize the participants and stratification will be performed to ensure balance between the groups within 2 strata (CEAP 2 and 3 and CEAP 4 to 6). A separate, blinded researcher will contact the participants by telephone to ensure allocation concealment during screening, consent and initial assessment. A study researcher responsible for implementation will apply the exercise program.

Patients in the TG will perform the exercise program as described in this protocol and will start 1 week after the initial evaluation. The patients in the CG group will continue their usual treatments (medication use, compression stockings and medical guidance). After 8 weeks of intervention, the patients will be reevaluated (using the same initial evaluation questionnaire) by the same blinded evaluator for each group. The primary outcomes will be calf muscle endurance and QOL and second outcomes will be exercise capacity, ROM electrical muscle activity and cardiac output. A final reassessment will be performed 8-weeks after the reevaluation, as shown in Figures 1 and 2.

All participants will receive educational information regarding the disease, as well as the usual care (hygiene and compressive techniques) and treatments to improve symptoms and quality of life (QOL).

Study setting

The evaluations will be performed at the Pneumocardiovascular laboratory, and the intervention program will be performed at the Physical Therapy Office, both located in the University Hospital of Natal/RN, Brazil.

Recruitment

Participants will be recruited at the medical clinic of the University Department of Clinical Medicine in the city of Natal/RN - Brazil. This outpatient facility has 5 physicians specialized in vascular surgery. The inclusion and exclusion criteria will be presented to the physicians personally. The physicians will be asked to refer all participants who meet the inclusion criteria for the study. All the participants will sign the informed consent form which will be explained by the evaluator before the evaluation.

Participants

Potential participants with stable CVI that meet the eligibility criteria have been recruited from the vascular surgery outpatient clinic. They have been invited to participate through an informed consent process. The initial evaluation will be performed by a blinded evaluator through a questionnaire that will include socio-demographic data, co-morbidities, time of CVI diagnosis, and detailed clinical and functional information. The disease classification will be based on the CEAP (clinical, etiology, anatomical, pathophysiology) criteria including: clinical manifestations (C), etiologic factors (E), anatomic distribution of disease (A), and underlying pathophysiologic findings (P) [4]. Ulcer morphological characteristics (if present), range of motion (ROM), exercise capacity, muscle endurance and parameters related to QOL will also be assessed.

All participants will sign the informed consent form that will be explained before the evaluation. During the functional tests, hemodynamic cardiac parameters (cardiac output, ejection fraction, and systolic volume) and bilateral electrical activity of the calf and tibialis anterior muscles will be assessed.

Eligibility criteria

The inclusion criteria for this study are male and female patients aged between 35-69 years, with chronic venous insufficiency diagnosed by venous vascular echo-Doppler (VED), CEAP between 2 to 6, and without Peripheral Arterial Disease (PAD) (ankle-brachial index < 0.9) [19]. The exclusion criteria for this study are participants who do not agree to participate, have ulcers > 4 cm diameter, or clinical signs and/or confirmed diagnosis of infection as well as the patients who already perform any type of self-reported supervised or unsupervised exercise programme (whereas exercise is a subset of physical activity that is both regular and structured) [20], are unable to attend physiotherapy sessions twice a week, and/or have co-morbidities incompatible with moderate to intense exercises [21] such as: acute or uncontrolled congestive heart failure, uncontrolled or unstable angina, uncontrolled cardiac dysrhythmia causing hemodynamic symptoms, severe symptomatic aortic stenosis, recent deep venous thrombosis, recent pulmonary embolism, acute pericarditis or myocarditis, dissecting aneurysms (known or suspected), unstable or uncontrolled blood pressure (systolic pressure > 160 mmHg, diastolic pressure > 100 mmHg), acute systemic infection, or uncontrolled diabetes, limiting musculoskeletal diseases, or difficulty to understand the activities.

Blinding

The researcher who will perform the initial and final evaluations will be blinded to the participants' allocation groups. The participants will be instructed not to make any comments regarding group allocation. The evaluator will not have access to the treatment site where the protocol will be performed to reduce the possibility of interfering with the blinding.

INTERVENTIONS

Exercise prescription

The exercise program will consist of 1) aerobic training; 2) strengthening; and 3) unsupervised stretching exercises performed at home. The cardiovascular exercises will be performed using a cycle ergometer and the rubber step. The muscle strengthening will be performed using resistive loads for the calf muscles. The participants will receive a written and illustrated guide for performing active stretching exercises of the calf and tibialis anterior muscles once a day for 20 seconds (each muscle group) at home 24 hours after supervision [22]. The exercise program will last ~40 minutes and will be performed twice a week, for a total of 16 sessions. The heart rate and blood pressure will be checked at the beginning and end of the training, as well as at the end of each series.

1. **Aerobic training**

a. Cycle ergometer exercise

 The perceived fatigue of the participants will be measured using the modified 0-10 BORG scale [23], every five minutes. The participants will warm up for 5 minutes on the cycle ergometer without load at the beginning of the protocol. Next, the participants will perform the cardiovascular exercises using the cycle ergometer for 15 minutes. The load will be adjusted at a setting up to moderate intensity (between 4 -6 of the modified BORG scale 0-10).

b. Bench step up exercise

 The bench step-up exercise will be performed on a rubber step at a height of 20 cm. The participants will be instructed to walk up and down on steps with one foot at a time using free cadence. They will be instructed to perform the movement as fast as possible for a maximal of 12 repetitions and exercise progression (5 to 10 repetition) will be weekly increased, according to individual tolerance.

The load during the program execution may be decreased, the rest time increased or the session interrupted if the subject reports very intense perceived fatigue (7 or above, BORG scale), complains of limiting pain, or develops symptoms incompatible with physical activity. The participants will perform only the exercises under supervision of the physiotherapist responsible for the study protocol. The patients showing exercise limitation due to pain, change in medication, undergo any alternative treatment, or miss 3 consecutive intervention sessions will be excluded. The data will be included in records for further analysis even after exclusion. Medical assistance will be provided to any participant who has an injury caused by the study in accordance with the resolution 466/12 of the National Health Council.

2. Resistance training

To strengthen and increase endurance of the calf muscle, the patients will perform at 80% of 1 RM. The submaximal load of 10 RM (repetition maximum) estimated percentage 80% of 1RM [24] will be individually calculated based on momentary muscle failure (inability to perform 10 concentric contractions without significant posture change and repetition velocity during changes against a certain resistance) [25]. To calculate the submaximal load of 10 RM, weight will be added until momentary muscle failure of the individual is achieved during calf raise exercises. The last load successfully lifted before momentary muscle failure will be used. The calculated load will be used to customize the training level and will be changed according to the patient´s weekly performance. The exercise will consist of 3 sets of 10 repetitions with a 1-minute rest interval. Successive load progression will be made during the program, maintaining the same volume according to the patient's performance. The exercises during the initial sessions will be performed without any load. The loads will be applied using an adjustable weight vest according to each patient.

Health education speeches

All the participants will be invited to attend an educational speech about the disease, risk factors, lifestyle changes, and lower limb care (hygiene, exercises, dressings), as well as the benefits of using compressive techniques. The speeches will be performed (immediately after the first assessment) by a blinded evaluator for allocation group who will perform the evaluations and reassessments.

Prescription for compression stockings

Compression stockings will be prescribed for those participants not using compressive techniques yet. Prescription will be based on clinical severity. CEAP C2-C3 compression of 20-30 mmHg, CEAP C4 to C6 30 to 40 mmHg compression and, patients with recurring ulcers compression of 40 to 50 mmHg [2]. Compliance (adherence to the use of socks) will be recorded daily in a notebook.

Strategies to improve adherence to intervention protocols

After the first session of the exercise program, the participants will receive a follow-up guide containing questions regarding compressive therapy, stretching and lower limb positioning during rest.

Relevant concomitant care and interventions that are permitted or prohibited during the trial:

Conventional treatment for control group

Conventional treatment will consist of health education speech, use of prescribed medication, compression stocking and medical guidance. The controls will be instructed to maintain their usual activities and treatments and not perform any type of supervised exercises during the 2 months after their first evaluation.

OUTCOMES

Primary outcome

Assessment of calf muscle endurance

The external cadence heel rise test [26] adapted to the bipodal position [27] will be used to assess calf muscle endurance. The calf muscle endurance will be assessed by the number of repetitions achieved during the test. The participants will be instructed to remain in an orthostatic position, barefoot with bipodal support. Their balance will be maintained through contact of the fingertips of the dominant hand on a wall with elbows flexed at 90°. Next, the participants will be asked to raise their heels from the floor. The evaluator will record the maximum height reached by the participant using a stadiometer and will explain to the participants that they should achieve the marking with their heads during the heel rise movement. The cadence of the test will be determined by a metronome (46 beats per minute) and they will be encouraged to perform as many heel rise movements as possible. The test will be interrupted in the following situations: if the participant does not reach maximum elevation for 2 consecutive times; transfers too much weight against the wall for 2 consecutive times; performs knee flexion for 2

consecutive times; or asks to interrupt the test [28]. Blood pressure and heart rate will be monitored at rest, immediately after the test and after a resting period post-test.

Quality of Life (QOL)

A Brazilian version of the VEINES-QOL (Venous Insufficiency Epidemiological and Economic Study-Quality of Life) questionnaire [29] will be used to assess the QOL. This instrument assesses 26 items: 10 symptom-related items, 9 items regarding daily life activities, 1 item related to the time of the day when the symptoms are more intense, 1 item regarding the changes due to the disease in the last year, and 5 questions about the psychological impact of the symptoms/disease. Symptoms, daily living limitations and psychological impact questions are related to the last 4 weeks. Each domain has a different scale and will be analyzed separately.

Secondary outcomes

Assessment of exercise capacity

The step test (ST) will be used to assess exercise capacity and will follow the recommendations previously published [30]. It will last 6 minutes (ST6), and the values of heart rate, systemic arterial pressure, dyspnea score by the modified BORG scale (0-10) and oxyhemoglobin saturation by a digital oximeter (SpO2%) will be registered at baseline and after the test. The number of steps will be used to analyze the participant climbing up and down (1 cycle of climbing up and down was counted as 1 step). A 20 cm tall rubber step will be used and the patient will be advised to wear comfortable clothing and shoes. The examiner will initially demonstrate how to perform the test. The subject should start the test using the right leg, followed by the left leg. To go down the step, the participant must follow the same order; first the right leg followed by the left leg, and then repeat the sequence at the given time. The participant will be instructed to perform the test as quickly as possible with free cadence and without discomfort. The test will be discontinued if heart rate (HR) exceeds 85% of age-predicted maximal HR [31], if the participant points to a value greater than seven on the modified BORG scale, or if the participant asks on their own initiative to finish the activity. If the participant reports fatigue or dyspnea they will be instructed to stop the test and rest on a chair. They will also be instructed to continue the test as soon as possible. During the resting period, the timer on the stopwatch will continue and the examiner should record the break. The patient will be verbally encouraged every minute without excess stimulation. The examiner will warn the subject with a clear "stop" message when 15 seconds are left. The same vital signs and symptom scores will be evaluated at the end of the test.

Ankle range of motion

The joint movement range will be measured using a simple goniometer. The measurements will be standardized for all the patients in a sitting position with knees extended and ankles initially at 90°. One arm of the goniometer will be positioned over the lateral malleolus, while the movable arm will be

positioned over the fifth metacarpal accompanying the entire ankle range for dorsiflexion and flexion-extension [32].

Electrical activity assessment

During the tests (external cadence heel rise test and the step test), electrical activity of the calf and tibialis anterior muscles will be assessed by superficial electromyography (SEM). The electrodes will be placed according to Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscle (SENIAM) guidelines for Surface ElectroMyoGraphy (SEMG) placement [33]. For the medial portion of the gastrocnemius muscle, the electrodes will be placed on the most prominent bulge of the muscle. For the tibialis anterior muscle, the electrodes will be placed at 1/3 of the line between the tip of the fibula and the tip of the medial malleolus. A signal-conditioning module (TeleMyo DTS desk Receiver® - Noraxon USA Inc., Scottsdale, USA) with 4 wireless sensors (Clinical DTS-Noraxon®, Noraxon, USA) will be used. The signals will be captured and stored using the MR 3.8 software (Noraxon USA Inc., Scottsdale, USA). The mean peak will be used to normalize the electrical signal [34], and the electromyographic signal will be analyzed at 4 moments (25%, 50%, 75% and 100%).

Cardiac output assessment

A non–invasive registering of cardiac output will be performed by a cardiograph through electrical impedance using the PhysioFlow® Q-Link equipment (Paris, France). This method has been shown to be valid and reliable at rest and during sub maximal exercise in patients with normal cardiorespiratory function [35]. The skin preparation and placement of the electrodes will be according to the manufacturer's recommendations. Following trichotomy, alcohol cleansing and abrasion with Nuprep® gel (Weaver, Aurora, Colorado, EUA), 6 transcutaneous electrodes (PhysioFlow PS-50, Manatec Biomedical, Macheren, France) will be placed on the upper region of the patients. Next, 2 emitting electrodes will be placed on the left base of the neck, above the supraclavicular fossa and 2 sensing electrodes will be placed below the xiphoid process on the right side of the patient. During the functional tests, the 2 sensing electrodes will be positioned in the paravertebral area, at the level of the xiphoid process. One electrode will be located in the middle of the sternum and the other at the left lateral chest wall (6th intercostal space) to conduct the electrocardiogram signal.

Sample size

The sample size will be calculated based on a pilot study with 8 patients (4 patients in each group) using a Manova test with repeated measures, within-between interaction with 2 groups and 2 measurements by analyzing calf endurance and the standard deviation of the number of repetitions from the pilot study. A two-tailed alpha error of 0.01 will be considered with a power of 80% considering clinical improvement for subjects with chronic venous disease after the supervised exercise protocol. The effect size will be calculated at the end of the protocol considering the number of repetitions in calf endurance test of all participants of the study. Moreover, considering a 20% loss to follow-up and a 5% missing data the

number of participants will be increased in at least 20% based on sample size. GPower (Germany) version 3.1- program will be used for statistical analysis.

Data collection, management and analysis

Data collection

The baseline and revaluation data will be collected by a trained physical therapist using a protocol for the outcomes related to the questionnaire (VEINES-QOL), demographic data, and CEAP classification. For the physical tests the evaluator will perform a brief orientation, allowing the patient to practice the movement before beginning the test.

A follow-up report will be available to all participants of the intervention group. It will include evaluation and re-evaluation information for the next medical appointment. The evaluator will refer to the subject's physician to identify those excluded from the study due to ankle-brachial index (ABI) values below 0.9 [19].

The data will be stored in 1 of the laboratory computers and a double entry will be performed by 2 study researchers. Access to the data will be limited to the study researchers and any other access must be authorized by the coordinator.

All data collected will be available on the evaluation form and in the proper computer file. Access to these data will be limited only to researchers with prior permission from the study coordinator. The exercise program will be supervised by a physical therapist with expertise in exercise physiology and experience in supervised exercises. All data regarding the treatment protocol will be registered in the subject's file and attached to the participants' medical charts.

The statistical analysis will be performed using the GraphPad Prism version 5.0 statistical package software (GraphPad Software Inc., San Diego, California, USA). The results of patient baseline characteristics and outcome variables (both primary and secondary) will be summarized using descriptive summary measures: expressed as mean (standard deviation) or median (range) for continuous variables and n (%) for categorical variables. The sample normality will be tested by the Shapiro-Wilk test. Treatment effects or differences between the study groups for primary and secondary outcomes will be analyzed by linear mixed model for group (usual care versus intervention) and time (baseline, 8-weeks and 12-weeks). As linear mixed models use all available data at each time point no missing data imputation will be performed. Age and BMI will be included as covariates by adding them to the regression model. The clinical classification CEAP will be included as covariate if randomization imbalance occurs. The analyses will be based on the intention-to-treat principle, including data of all randomized participants with at least one outcome measure. The significance level will be set at 95% ($p<0.05$). All participants will be included in the analysis of the original groups following the CONSORT recommendations.

Discussion

Several observational studies have reported that participants with CVI have inadequate calf muscle pumping [14]. Calf muscle pumping is the primary mechanism to promote blood return from the lower limbs to the heart. During exercise, the calf muscle (gastrocnemius and soleus) contract and compress the deep intramuscular veins which increases venous pressure and increase blood flow from the deep venous system to the heart. This efficacy of this mechanism depends on talocrural mobility, vein competence, and the contraction strength of the calf muscle [14].

Studies have shown the physical and QOL benefits of exercise therapy for patients with CVI. Despite positive results, this training modality is not widely used for this population. Few researchers have shown the beneficial effects of different supervised or domiciliary exercise modalities on specific parameters such as improved calf muscle pumping [13-15], increased mean peak torque [13], improvement in disease severity [17], increased ankle joint movement [14], and improved calf muscle resistance [15]. The authors believe that the study results will promote preliminary evidence to help health professionals indicate, prescribe and execute supervised exercises for treating symptoms in participants with CVI.

Trials status

Protocol version

07/08/2019– version 1

The first patient will be recruited in January 2020.

The last patient will be recruited in May 2020.

List Of Abbreviations

CVI – Chronic Venous Insufficiency

TG – Treatment group

CG – Control group

ST6 – Step test 6

ROM – range of motion

VED – Vascular Echo-Doppler

PAD – Peripheral arterial disease

ACSM – American College of Sports Medicine

SEM – Superficial electromyography

ABI – ankle-brachial index

Declarations

Ethics approval and consent to participate

The study was approved by the ethics and research committee of the responsible institution (number 1.541.241). The consent form model followed the Brazilian model for informed consent and was approved by the responsible ethics committee.

Trial registration

The trial was registered in Brazilian clinical trial database RBR-57xtk7. All items from the World Health Organization Trial Registration Data Set was fulfilled.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EV was responsible for reviewing the literature, the development of the intervention protocol and for writing the full manuscript. VR was responsible for the development of the intervention protocol and

reviewing the full manuscript.   AS will perform the blind evaluation. LG was responsible for writing and reviewing the full manuscript. GF was responsible for the final review and approval of the manuscript.

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Figures

Inclusion

Eligibility assessment

Excluded

Randomized

Health education speech Intervention group

Allocation

Health education speech Control group

Re-evaluation after 8 weeks

Analysis

Re-evaluation after 8 weeks

Re-evaluation after 16 weeks

Analysis

Re-evaluation after 16 weeks
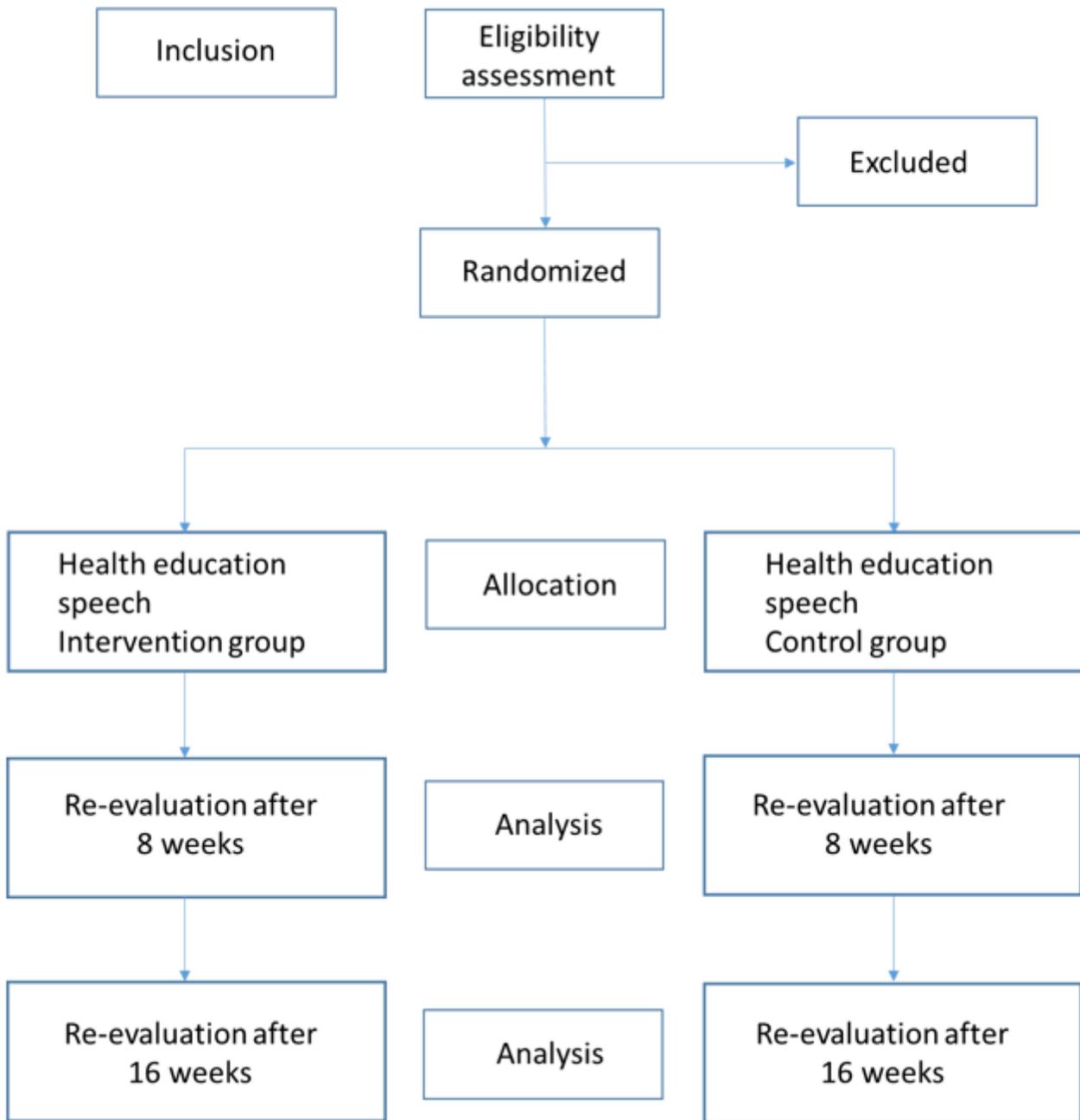
Figure 1

Trial Design

TIME POINT	STUDY PERIOD				
	Evaluation	Baseline	Session 1-16	Re-evaluation (8-weeks)	Follow up (16-weeks)
ENROLMENT					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTION					
Health education speech		X			
Exercise programme treatment (Intervention group)			X		
Usual care treatment (Control Group)			X		
ASSESSMENT					
Strength and endurance of plantar flexors	X			X	X
Quality of Life	X			X	X
Exercise Capacity	X			X	X
Range of motion	X			X	X

Figure 2

Overview of assessment. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure showing the schedule of enrollment, interventions, and assessment

Supplementary Files

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

- SPIRIT.pdf