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

Esther Tinoco Volpe

Universidade Federal do Rio Grande do Norte

Vanessa Regiane Resqueti

Universidade Federal do Rio Grande do Norte

Ana Aline Marcelino Silva

Universidade Federal do Rio Grande do Norte

Lucien Peroni Gualdi

Faculdade de Ciências da Saúde do Trairi

Guilherme Augusto de Freitas Fregonezi

Universidade Federal do Rio Grande do Norte

Method Article

Keywords: Exercise, Resistance Training, Exercise Therapy, Venous Insufficiency, Randomized Controlled Trial, Rehabilitation

Abstract

Background: Triceps surae muscle changes and range of motion decrease resulting from pathophysiological changes seen in subjects with CVI leading to important impairment of functional activities related to lower limbs in these individuals. Several studies have shown the benefits of exercise therapy focusing on triceps surae muscle strengthening to improve calf muscle pumping. Randomized studies using exercise programmes for lower limbs in subjects with CVI are still rare in the literature, leading to a weak indication of this modality to treat this population. The aim of this study is to investigate the effects of a supervised exercise programme to improve functional capacity and the quality of life in individuals with CVI.

Methods: This is an evaluator-blinded randomized clinical trial. Individuals will be randomly allocated in two groups: 1) treatment group (TG), in which they will be submitted to a supervised exercise programme for lower limbs; 2) control group (CG), in which the same treatment will be maintained but without the performance of any supervised exercise modality. Participants from both groups will participate in a health education speech. The study will compare the evaluation and reevaluation results between subjects submitted to the exercise programme and the control group by the following outcomes: range of motion, calf muscle endurance by the heel rise test, physical capacity by the step test (ST6), and quality of life by the VEINES-QOL.

Discussion: Calf muscle function can be improved in people with venous disease with significant improvements in functional capacity, supervised exercise programme will provide much needed information on management of this chronic disease to promote health and independence in this population.

Trial registration: The study was registered on the Brazilian Clinical Trials Database (REBEC) (RBR57xtk7). The results will be disseminated by scientific events presentations and publication in peer reviewed journals.

Keywords: Exercise, Resistance Training, Exercise Therapy, Venous Insufficiency, Randomized Controlled Trial, Rehabilitation.

Background

Chronic venous disease is a common health problem that may result in significant morbidity/mortality [1]. Its development occurs when venous pressure is increased and blood return is impaired by several mechanisms. The disturbance may be a consequence of valve incompetence of superficial or deep veins, perforating veins, venous obstruction or a combination of both mechanisms, leading to overall or local venous hypertension, mainly during standing up or ambulation, contributing to macro or microcirculatory hemodynamic disturbances [2] and focused tissue ischemia [3]. Chronic venous disease includes a wide range of clinical signs varying from varicose veins and uncomplicated telangiectasia to venous ulcerations [1,4]. Chronic venous insufficiency (CVI) is the most common venous disease, and generally

refers to skin changes associated to sustained venous hypertension. It is defined as an abnormality of venous system function caused by valve incompetence associated or not to venous flow obstruction [2,4].

These individuals may develop musculoskeletal changes, mainly in the triceps surae muscle such as muscle fiber atrophy [5], leading to abnormal cadence [6] and muscle strength and function reduction [7]. A decrease in the skeletal muscle pumping function worsens venous hypertension, leading to excessive accumulation of liquid and fibrinogen in subcutaneous tissue, resulting in edema and/or lipodermatosclerosis, and may also result in the development of venous ulcers [2,8,9]. Additionally, the movement of the ankle joint is decreased [10], and along with other factors such as high body mass index, smoking habit, skin changes and deep veins reflux, is also associated to a higher risk for the advance of venous ulcers, while satisfactory ankle dorsiflexion and effective function of calf muscle pumping have been identified as protection factors [11].

Effective calf muscle pumping, even in the presence of valve dysfunction or venous obstruction, may develop a compensation mechanism and thereby decrease CVI symptoms. Some studies have shown the benefits of exercise therapy in subjects with CVI with an emphasis on strengthening the triceps surae muscle for improving the calf muscle pumping function [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 strengthening and stretching exercise programme in lower limbs [13], and after eight consecutive days of isometric strengthening and resistance exercises to the triceps surae muscle [15] in subjects with CVI. Other authors [16,17] have highlighted the importance of progressive resistance exercises and supervised aerobic training to promote ulcer healing and to improve cutaneous microvascular reactivity in subjects with CVI.

A systematic review [18] regarding physical exercise for the treatment of CVI without ulcer found only two studies that met the quality criteria for eligibility after filtering for the exclusion criteria. Both studies concluded that physical exercise was able to induce an increase of venous filling time and ejection fraction indicating an improvement in venous hemodynamics. Nevertheless, the evidence quality was considered very low with high bias risk in both studies. Considering that exercises are routinely prescribed for other cardiovascular diseases such as peripheral obstructive arterial disease and coronary artery disease [17] and that evidence-based exercise programmes tested in CVI subjects remain scarce, we aim to assess the efficacy of a supervised exercise programme to improve functional capacity and quality of life in subjects with CVI.

Hypotheses

We hypothesized that a supervised triceps surae muscle-training program in subjects with CVI will improve the functional capacity and health-related quality of life in these individuals.

Methods

Trial design

This is an evaluator-blinded randomized controlled clinical trial with the parallel group, two arms, superiority trial with 1:1 allocation ratio.

Study setting

Evaluations will be performed at the Pneumocardiovascular laboratory, and the intervention programme will be performed at the Physical Therapy Office, both located in a University Hospital in the city of Natal/RN, Brazil.

Participants

Patients with stable CVI that meet the eligibility criteria will be evaluated by a blinded evaluator through a questionnaire that will include socio-demographic data, associated diagnoses, time of CVI diagnosis, detailed clinical and functional information. Disease classification according to CEAP criteria, ulcer morphological characteristics (if present), range of ankle motion (ROAM), functional capacity, endurance muscle and issues related to quality of life (VEINES-QOL) will also be assessed. All participants will sign the informed consent form that will be explained by the evaluator before the evaluation. During functional tests, hemodynamic cardiac parameters (cardiac output, ejection fraction and systolic volume) and bilateral electrical activity of the triceps surae and tibialis anterior muscles will be assessed.

Design

Evaluations will start in January 2019, and the exercise programme will be performed in the next two months. After evaluation, subjects will be randomly allocated into two evaluator-blinded groups. All individuals will receive educational information regarding the disease, as well as the available care and treatments to improve symptoms and health-related quality of life (HRQoL). Patients allocated into the treatment group (TG) will receive physiotherapeutic treatment, performing the exercise programme proposed by the peripheral vascular physiotherapy outpatient clinic. The exercise programme will start one week after the initial evaluation. The control group (CG) participants will remain in their usual treatments. After eight weeks of intervention, the individuals will be reevaluated (using the same initial evaluation questionnaire) by the same blinded evaluator for the allocation group. Another assessment will be performed after eight weeks from the reevaluation, as shown in Figure 1 and 2.

Population

Individuals of both genders aged between 35 and 69 years old, with chronic venous insufficiency diagnosis through venous vascular echo-Doppler examination, CEAP criteria between 2 to 6, without Peripheral Arterial Disease (PAD) (ankle-brachial index of ≤ 0.9) [19] will be included in the study. Subjects who do not agree to participate in the study, present ulcers with diameter greater than 4 cm or with clinical signs and/or confirmed diagnosis of infection will be excluded in the study. Individuals unable to attend the physiotherapy service twice a week and/or who present clinical manifestations that

are incompatible with moderate to intense exercises [20] 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, as well as subjects with limiting musculoskeletal diseases or difficulty to understand the activities will be also excluded.

Sample size

The sample size is based on a prior study conducted by the authors using the difference between two independent means and the standard deviation of the heel rise test. Calculated effect size was 1.67. An α error of 0.05 and 95% power were considered. After the analysis the final sample size resulted in 18 subjects. The G*Power version 3.1 statistics program was used.

Recruitment

Subjects 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 five physicians specialized in vascular surgery, and inclusion and exclusion criteria will be presented to the physicians by personal contact. Physicians will be asked to refer all subjects who meet the inclusion criteria for the study. All participants will sign the informed consent form that will be explained by the evaluator before the evaluation.

Randomization and group allocation

The *randomization.com* program will be used by the researcher responsible for the study to randomize the participants. The program will randomly allocate individuals into two groups (control or treatment). Stratification procedures to ensure the balance between the groups in two strata (CEAP 2 and 3) and (CEAP 4 to 6) will be used. The subjects will be able to access the randomization result after the end of the evaluation. The responsible researcher will contact the individuals by telephone to initiate treatment.

Blinding

The researcher who will perform the initial and final evaluations will be blinded to the subjects' allocation groups. 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 applied to reduce the possibility of interfering with their blinding.

Non-blinding will not be allowed and the evaluator will have no access to the allocation group until the end of the study.

INTERVENTIONS

Health education speeches

All subjects will be invited to participate in 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 by a physical therapist. Compression stocking for those subjects that are not using compressive techniques will be prescribed based on clinical severity with 20 to 30 mmHg for patients with CEAP C2 to C3, 30 to 40 mmHg for those with CEAP C4 to C6, and 40 to 50 mmHg for those with recurring ulcers [2]. and the compliance will be accompanied by a daily notebook.

Exercise prescription

The exercise programme will consist of aerobic training, strengthening, step-up/down exercises and flexibility. Aerobic exercises will be performed using an ergometric bicycle and/or a cycle ergometer. Muscle strengthening will be performed through resistive load for the triceps surae muscles. Subjects will receive a written and illustrated guide for performing active stretching of triceps surae and tibialis anterior muscles at home 24 hours after supervised training [21]. The exercise programme will last around 40 minutes and will be performed twice a week, totaling 16 exercise sessions. 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. The individual will be asked about perceived fatigue measured by the modified 0-10 BORG scale [22]. Subjects will perform 5 minutes on the bicycle without load at the beginning of the protocol for warm-up. Next, subjects will perform aerobic training using the bicycle for 15 minutes. The load will be set to reach moderate intensity (between 4 and 6 of the modified BORG scale 0-10). For strengthening of the triceps surae muscles, individuals will perform calf raise exercises in its full range. Submaximal load will be individually calculated based on momentary muscle failure (characterized as the inability to perform concentric contraction without significant posture change and repetition during changes against a certain resistance) and exercise prescription following the standardization of 3 sets of 10 repetitions. The exercises during initial sessions will be performed without any load. Successive load progression will be made maintaining the same volume according to the patient's performance. The load will be applied using an adjustable weight vest, according to the calculation made for each subject. The bench step-up exercise will be performed on a rubber step at a height of 20 cm. Subjects will be instructed to go up and down on the step with one foot at a time using free cadence. They will be instructed to perform the movement as fast as possible for 12 repetitions. Progression will be according to individual tolerance. The load during the programme execution may be decreased, the rest time increased or the session interrupted if the subject reports very intense perceived fatigue (7 or above) through the BORG scale, complains of limiting pain or presents any symptoms which are incompatible with physical activity. Participants will only perform exercises supervised by the physiotherapist responsible for the study protocol. Individuals showing exercise limitation due to pain, those who changed usual medication, submitted to any alternative treatment or those who miss three consecutive intervention sessions will be excluded from the study. Collected data will be included in the database for further analysis even after exclusion. Medical assistance will be provided to any participant who presents any injury caused by the study participation in accordance with the resolution 466/12 of the National Health Council.

Strategies to improve adherence to intervention protocols

Subjects will receive a follow-up guide containing questions regarding compressive therapy, stretching and lower limb positioning during rest.

Concomitant care

Controls will be instructed not to perform any type of supervised exercise during the two months following their first evaluation. During this period, individuals (independent of the allocation group) will not be able to perform any elective surgery or other treatment modality for venous disease other than the one usually used.

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

Controls will be instructed to be instructed to maintain their usual activities and treatments. During this period, individuals (independent of the allocation group) who need to perform some type of elective surgery or other treatment modality for venous disease other than the usually prescribed treatment, will be withdrawn from the study.

OUTCOMES

Ankle range of motion

Joint movement range will be measured using a simple goniometer. Measurements will be standardized for all patients through sitting position with their knees extended and their ankles initially at 90º. 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 [23].

Assessment of calf muscle endurance

The external cadence heel rise test [24] adapted to bipodal position [25] will be used to assess calf muscle endurance. Subjects will be instructed to remain in an orthostatic position, barefoot with bipodal support. Their balance will be maintained through contact of the dominant hand fingertips on the wall with their elbows flexed at 90°. Individuals will be asked to raise their heels from the floor to the maximum amplitude they can achieve. The evaluator will record the maximum height reached by the participant using a stadiometer and will demonstrate the test explaining to the subjects that they should achieve the marking with their heads during the heel rise movement. The test pace will be determined by the participants and they will be encouraged to perform as many heel rise movements as they can. The test will be interrupted in the following situations: if the subject does not reach maximum elevation for two consecutive times; transfers too much weight against the wall for two consecutive times; performs knee flexion for two consecutive times; or asks to interrupt the test [26]. Blood pressure and heart rate will be monitored at rest, immediately after the test and after a resting period post-test.

During the test, electrical activity of the triceps surae and tibialis anterior muscles will be assessed by superficial electromyography (SEM). The electrodes will be placed according to SENIAM guidelines for

EMG placement [27]. 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 four wireless sensors (Clinical DTS-Noraxon®, Noraxon, USA) will be used. Signals will be captured and stored by MR 3.8 software (Noraxon USA Inc., Scottsdale, USA). The peak mean will be used as a form of normalizing the electrical signal [28], and the electromyographic signal will be analyzed at four moments (25%, 50%, 75% and 100%).

Non−invasive registering of cardiac output will be performed by a cardiograph through electrical impedance using PhysioFlow® Q-Link equipment (Paris, France). This method has been shown to be valid and reliable at rest and during submaximal exercise in patients with normal cardiorespiratory function [29]. Skin preparation and placement of the electrodes will follow the manufacturer's recommendations. Following trichotomy, alcohol cleansing and abrasion with Nuprep gel, six transcutaneous electrodes (PhysioFlow PS-50, Manatec Biomedical, Macheren, France) will be placed on the upper region of the subjects. Two emitting electrodes will be applied at the left base of the neck, above the supraclavicular fossa. Two sensing electrodes will be put below the xiphoid process on the right side of the subject. During the functional tests, the two 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 one at the left lateral chest wall (sixth intercostal space) to conduct the electrocardiogram signal.

Assessment of functional capacity

The step test (ST) will be used to assess functional capacity. The test will be applied to assess physical performance and will follow the recommendations previously published [30]. The test 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 (SpO_2%) will be assessed at baseline and after the test. A 20 cm height rubber step will be used in the test. The subject will be advised to wear comfortable clothing and shoes. The examiner will initially demonstrate how to perform the test. The individual should start the test using the right leg, followed by the left leg. To go down the step, the individual must follow the same order; first the right leg followed by the left leg, and then repeat the sequence at the given time. The subject 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 maximal HR, if the subject points to a value greater than seven on the modified BORG scale, or if the subject asks on their own initiative to finish the activity. If the subject 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 stopwatch will not be stopped and the examiner should record the intercurrence. Verbal stimuli will be standardized every minute without super stimulation. The test the examiner will warn the individual with a clear "stop" message with 15 seconds left to finish. The same vital signs and symptom scores will be evaluated at the end of the test. Electrical activity of tibial anterior

and gastrocnemius muscles will be assessed by SEM. Cardiac output will be also registered during the test.

Quality of Life Related to Health (HRQoL)

A Portuguese version of the VEINES-QOL questionnaire [31] will be applied to assess quality of life. This instrument assesses 26 items: 10 symptom-related items, 9 items regarding daily life activities, one item related to the time of the day when the symptoms are more intense, one item regarding the changes occurred due to the disease in the last year, and five questions about the psychological impact of the symptoms/disease. Symptoms, daily living limitations and psychological impact questions are related to the last four weeks.

Allocation

Sequence generation

The randomization.com program will be used by the researcher responsible for the study to randomize the participants. The program will randomly allocate individuals into two groups (control or treatment). Stratification procedures to ensure the balance between the groups in two strata (CEAP 2 and 3) and (CEAP 4 to 6) will be used. The subjects will be able to access the randomization result after the end of the evaluation. The responsible researcher will contact the individuals by telephone to initiate the treatment.

Concealment mechanism

The researcher responsible for the study will contact subjects to initiate the treatment by phone.

Implementation

The researcher responsible for the study will generate the allocation sequence, subjects' enrollment in the physical therapy service and the exercise programme application.

Data collection, management and analysis

Data collection

Baseline and revaluation data will be collected by a previously-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 individual to train the movement before beginning the test.

A follow-up report will be available to all subjects of the intervention group. The document will include evaluation and re-evaluation information for the next medical appointment. The evaluator will refer to the

individual's physician for those excluded from the study due to ABI (ankle-brachial index) above or below pre-established values.

Data will be stored in one of the laboratory computers and double entry will be performed by two study researchers. Data access will be limited to the study researchers and any other access must be authorized by the coordinator.

The electrode positioning on the tibialis anterior and medial gastrocmenium muscles will follow the recommendations of superficial electromyography for non-invasive muscle evaluation (SENIAM) from the European Union Biomedical health and research program. Signs and signals will be captured and stored by MR 3.8 software (Noraxon U.S.A. Inc Scottsdale, USA). Data regarding cardiography through electrical impedance will be collected according to the manufacturer's recommendations (PhysioFlow Q-Link). 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 having previous permission from the study coordinator. The exercise programme will be developed by a physical therapist with expertise in exercise physiology and with previous experience in supervised exercises. Data regarding the treatment protocol will be registered in the individual's file and attached to the subjects' medical charts.

Statistical analysis will be performed by using the GraphPad Prism version 5.0 statistical package software (GraphPad Software Inc., San Diego, California, USA). Sample normality will be tested by the Shapiro-Wilk test. Intergroup and intragroup differences will be analyzed by using Two-way ANOVA followed by the Bonferroni post-hoc test. The significance level will be set at 95% ($p < 0.05$). All individuals will be included in the analysis of the original groups following the CONSORT recommendations.

Discussion

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

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

Abbreviations

CVI – Chronic Venous Insufficiency

TG – Treatment group

CG – Control group

ST6 – Step test 6

ROAM – range of ankle motion

PAD – Peripheral arterial disease

ACSM – American College of Sports Medicine

SEM – Superficial electromyography

ABI – ankle-brachial index

Declarations

Trials status

Protocol version

28/10/2018– version 1

The first patient will be recruited in January 2019.

The last patient will be recruited in May 2019.

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.

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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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Authors' information

EV[1,2], VR[1,2], AS[1,2], LP[1,3], GF[1,2]

1. PneumoCardioVascular Lab/HUOL Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERRH) Departamento de Fisioterapia Universidade Federal do Rio Grande do Norte, Natal, Rio Grande do Norte, Brasil; 2. Laboratório de Inovação Tecnológica em Reabilitação, Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte, Natal, Rio Grande do Norte, Brasil; 3. Faculdade de Ciências da Saúde do Trairi, Universidade Federal do Rio Grande do Norte (UFRN), Santa Cruz, Rio Grande do Norte, Brasil.

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Figures
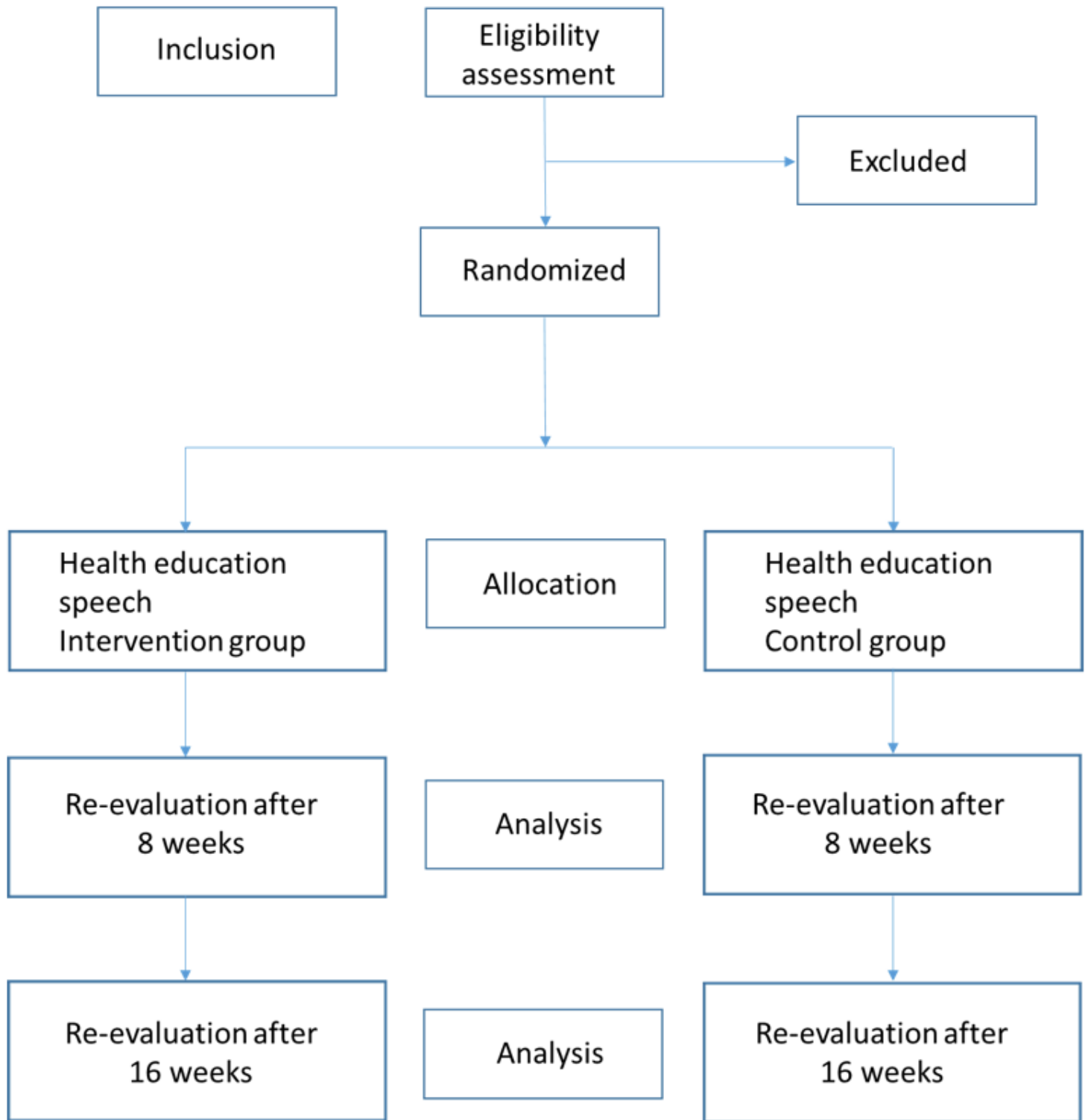
Figure 1

Trial Design.

| | **STUDY PERIOD** | | | | |
	-t_1 (evaluation)	0	Session 1-16	t_1 (re-evaluation)	t_2 (re-evaluation)
ENROLMENT:					
Eligibility screen	x				
Informed consente	x				
Allocation		x			
INTERVENTIONS					
Health education speech		x			
The exercise programme			x		
ASSESSMENT					
Range of motion	x			x	x
Physical performance	x			x	x
Physical capacity	x			x	x
Quality of life	x			x	x

Figure 2

Overview of Assessment.