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Robotic rehabilitation in stroke patients: a protocol of a randomized clinical trial

Reabilitação robótica em pacientes com AVC: protocolo de ensaio clínico randomizado

Rehabilitación robótica en pacientes con ACV: un protocolo de ensayo clínico aleatorizado

Andrieli Barbieri Garlet[1], Rodrigo Della Méa Plentz[2], Ariane Haydee Estrada Gamarra Blauth[3], Thiago Tagliani Righi[4], Natiele Camponogara Righi[5], Jociane Schardong[6]

ABSTRACT | The aim of this study was to propose a randomized clinical trial protocol to evaluate the effect of robotic rehabilitation on the functionality of patients with subacute stroke. This is a protocol of a randomized clinical trial that will be developed at hospital and rehabilitation center of Pavilhão Pereira Filho of ISCMPA. We will recruit 40 patients with stroke, all genders, aged between 18 and 85 years and showing hemiparesis or muscle weakness (Medical Research Council- MRC<48 points), who will be randomized to a control group or intervention group. The intervention group—besides conventional physical therapy—will perform robotic rehabilitation using Erigo® equipment. The control group, in its turn, will receive conventional physical therapy executing exercises with similar movements to those performed on the robot. Interventions will occur every day during hospital phase and three times/week after discharge, totaling approximately 18 sessions. Functioning will be considered the primary outcome of the study and will be assessed using the Fugl-Meyer scale. As secondary outcomes, we considered: muscle strength (MRC and maximum repetition test); spasticity (modified Ashworth scale); quadriceps muscle architecture and echogenicity (ultrasound); mobility (timed up go test); degree of disability and dependence (Rankin scale and Functional Independence Measure); quality of life (EQ-5D questionnaire); cardiorespiratory repercussions (monitoring vital signs); length of hospital stay (in days); and mortality (number of deaths). The groups will be evaluated before the interventions, after the 10th session, and at the end of six weeks of treatment or 18 sessions.

Keywords | Stroke; Robotics; Clinical Trial.

RESUMO | O objetivo deste estudo foi propor um protocolo de ensaio clínico randomizado para avaliar o efeito da reabilitação robótica sobre a funcionalidade de pacientes com acidente vascular cerebral (AVC) subagudo. Trata-se de um protocolo de um ensaio clínico randomizado que será desenvolvido no hospital e centro de reabilitação do Pavilhão Pereira Filho da Irmandade da Santa Casa de Misericórdia de Porto Alegre (ISCMPA). Quarenta pacientes com AVC, de ambos os sexos, com idades entre 18 e 85 anos e que apresentem hemiparesia ou fraqueza muscular (Medical Research Council – MRC <48 pontos) serão divididos aleatoriamente em grupo controle ou grupo de intervenção. O grupo de intervenção será aquele que realizará reabilitação robótica utilizando equipamento Erigo®, além da fisioterapia convencional, e o grupo controle receberá fisioterapia convencional por meio de exercícios com movimentos semelhantes aos realizados no robô. As intervenções ocorrerão todos os dias na fase hospitalar e, após a alta,

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[1]Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) – Porto Alegre (RS), Brazil. E-mail: abgarlet@gmail.com. ORCID-0000-0003-2399-5867
[2]Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) – Porto Alegre (RS), Brazil. E-mail: roplentz@yahoo.com.br. ORCID-0000-0002-2662-8192
[3]Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) – Porto Alegre (RS), Brazil. E-mail: ariane.gamarra@santacasa.org.br. ORCID-0000-0003-2062-6353
[4]Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) – Porto Alegre (RS), Brazil. E-mail: thiagotagliani@hotmail.com. ORCID-0000-0001-6444-2092
[5]Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) – Porto Alegre (RS), Brazil. E-mail: natirighi@gmail.com. ORCID-0000-0001-7621-7204
[6]Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA) – Porto Alegre (RS), Brazil. E-mail: joci_fisioufsm@yahoo.com.br. ORCID-0000-0003-3635-8541

Corresponding address: Jociane Schardong – Rua Professor Annes Dias, 295 – Porto Alegre (RS), Brazil – ZIP Code: 90020-090 – E-mail: joci_fisioufsm@yahoo.com.br –
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três vezes por semana, totalizando aproximadamente 18 sessões. A funcionalidade será considerada o desfecho primário do estudo e será avaliada por meio da escala de Fugl-Meyer. Consideramos como desfechos secundários a força muscular (MRC e teste de repetição máxima), espasticidade (escala de Ashworth modificada), arquitetura do músculo quadríceps e ecogenicidade (ultrassom), mobilidade (teste *timed up and go*), grau de incapacidade e dependência (escala de Rankin e de medida de independência funcional), qualidade de vida (questionário EQ-5D), repercussões cardiorrespiratórias (monitoramento de sinais vitais), tempo de internação (em dias) e mortalidade (número de óbitos). Os grupos serão avaliados antes das intervenções, após a décima sessão e ao final de seis semanas de tratamento ou 18 sessões.
Descritores | Acidente Vascular Cerebral; Robótica; Ensaio Clínico.

RESUMEN | El objetivo de este estudio fue proponer un protocolo de ensayo clínico aleatorizado para evaluar el efecto de la rehabilitación robótica en la funcionalidad de pacientes con accidente cerebrovascular subagudo. Se trata de un protocolo de ensayo clínico aleatorizado que será desarrollado en el hospital y centro de rehabilitación del Pavilhão Pereira Filho da Irmandade de la Santa Casa de Misericórdia de Porto Alegre (ISCMPA). Se asignarán aleatoriamente a cuarenta pacientes con ACV, de ambos sexos, con edades entre 18 y 85 años, que presenten hemiparesia o debilidad muscular (Medical Research Council – MRC <48 puntos) a un grupo de control o grupo de intervención. El grupo de intervención realizará rehabilitación robótica utilizando la herramienta Erigo® y fisioterapia convencional, mientras que el grupo de control recibirá fisioterapia convencional mediante ejercicios con movimientos similares a los realizados en el robot. Las intervenciones se realizarán todos los días durante la fase hospitalaria y, tras el alta, tres veces por semana, totalizando aproximadamente 18 sesiones. La funcionalidad se considerará el resultado primario del estudio y se evaluará mediante la escala de Fugl-Meyer. Se consideraron como resultados secundarios la fuerza muscular (MRC y test de máxima repetición), la espasticidad (escala de Ashworth modificada), la arquitectura del músculo cuádriceps y ecogenicidad (ultrasonido), la movilidad (test *timed up and go*), el grado de discapacidad y dependencia (escala de Rankin y medida de independencia funcional), la calidad de vida (cuestionario EQ-5D), la repercusión cardiorrespiratoria (seguimiento de constantes vitales), la estancia hospitalaria (en días) y la mortalidad (número de defunciones). Los grupos serán evaluados antes de las intervenciones, después de la décima sesión y al final de las seis semanas de tratamiento, es decir, 18 sesiones.
Palabras clave | Accidente Cerebrovascular; Robótica; Ensayo Clínico.

INTRODUCTION

Stroke is among the most prevalent cardiovascular diseases worldwide, and in Brazil it represents 20.73% of cases of hospitalization in patients over 40 years, strongly impacting the costs to the health system[1]. Affected patients have different functional impairments, depending on the location on the brain and the type of injury. Motor paralysis (or paresis) are the main outcomes that damage the execution of activities of daily living[2], impairing quality of life[3].

The rehabilitation process, including physical therapy should be started as early as possible, once the patient is hemodynamically stable. Prolonged bed rest—besides causing muscle atrophy and deconditioning—affects adequate cerebral blood flow. Such long-term changes may affect the sympathetic nervous system and contribute to intolerance to orthostasis[4,5]. Early rehabilitation, besides reducing complications resulting from prolonged bed rest, stimulates the afferent sensory nervous system and reduces spasticity in patients[6]. In this context, innovations in the rehabilitation process and early interventions are necessary, since they can improve patient care in the subacute stroke.

The robotic board emerges as a new ergonomic technology, facilitating lower limb exercises using a robot associated with neuromuscular electrical stimulation (NMES)[6]. It is a resource that allows passive orthostasis up to 90º, as well as the passive movement of knees and hips[7]. Among the benefits of orthostasis are: biomechanical alignment—with stretching and unloading of weight in the joints—optimization of volumes and lung expansion; and spatial information on adjustments to the central nervous system allowing better stimuli and autonomic adaptations[8].

The Erigo® robotic board (Hocoma, Volketswil, Switzerland) proved to be a safe and effective device for stroke patients[9,10]. However, the literature lacks robust evidence with well-defined protocols that can be reproducible and that contain adequate sample size. Thus, to implement this resource in rehabilitation centers, further studies need to assess the effects of this therapy on stroke patients.

The aim of this study was to propose a randomized clinical trial protocol to evaluate the effect of robot-assisted orthostatic board training and neuromuscular electrical stimulation (robotic rehabilitation) on the functionality of patients with subacute stroke. The protocol considers several

aspects: functioning; muscle strength; spasticity; quadriceps muscle architecture and echogenicity; mobility; degree of disability and dependence; quality of life; cardiorespiratory repercussions; length of hospital stay; and mortality.

METHODOLOGY

Design and ethical aspects

The study was designed as a randomized, single-blind clinical trial. The research protocol was registered at ClinicalTrials.gov (NCT04494685). All patients will sign the informed consent form before any procedure and in the case of incapacity, the consent will be provided by the relative.

Any changes that occur in the study protocol during the recruitment of volunteers or data collection will be communicated to the institution's Research Ethics Committee and ClinicalTrials.gov.

Participants

The study population consists of stroke patients. The sample will consist of patients with ischemic stroke, in the subacute phase (48 hours after the event), admitted to Hospital São José in the ISCMPA hospital complex. They are patients of all genders, aged from 18 to 85 years and who have hemiparesis or muscle weakness defined by the Medical Research Council (MRC) with a score of <48 points[11]. Moreover, the selected patients must be able to understand simple commands and report signs of discomfort. Neither a history of stroke without motor sequelae prior to current hospitalization, nor the need for ventilatory support or tracheostomy will be considered exclusion criteria.

Patients with an evolution from ischemic to hemorrhagic events, and those who do not develop compensatory hemodynamic adjustments after the postural change in the orthostatic board, or who present significant hemodynamic changes during the training, will be excluded.

Randomization

Randomization will be conducted using www.randomization.com website. The sequence of numbers will be generated by a blind researcher, at a 1:1 ratio. The sequence of numbers will be revealed to the physical therapists who will conduct the proposed protocols only at the beginning of the intervention program to guarantee the concealment of the allocation. Patients will be randomized to the control group (CG)—receiving conventional physical therapy—or to the intervention group (IG), which will perform both: robotic rehabilitation using Erigo® equipment (Hocoma, Volketswil, Switzerland) and conventional physical therapy.

Outcomes and evaluations

Functional independence will be considered the primary outcome of the study. Muscle strength, spasticity, quadriceps muscle architecture and echogenicity, mobility, degree of disability and dependence after stroke, quality of life, cardiorespiratory repercussions, length of hospital stay, and mortality will be measured as secondary outcomes.

Prior to the evaluations, medical records will be consulted to collect personal, demographic, anthropometric data, medical diagnosis, previous comorbidities, and information on medications used by patients.

Functioning evaluation

Functioning will be assessed using the Fugl-Meyer scale. This scale allows assessing the mobility and the ability to perform different activities that require from sensorimotor functions to walking after stroke. It consists of six domains: range of motion; pain; sensitivity; motor function of the upper and lower extremities; balance; coordination; and speed. The score for each item ranges from 0 to 2, where 0=cannot be performed; 1=partially accomplished; 2=completely accomplished. The total score ranges from 0 to 266 points. The higher the score the better is the functioning. Less than 50 points in the score indicate severe motor impairment, 50–84 marked, 85–95 moderate, and 96–99 light, patients must have at least moderate impairment to be enrolled in the study[12].

Muscle strength evaluation

For the evaluation of muscular strength, the Medical Research Council (MRC) scale and the maximum repetition test (1RM) will be used.

The MRC scale comprises a score ranging from 1 to 5 for each muscle group, as follows: 0=no contraction, 1=flicker or trace contraction; 2=active movement, with gravity eliminated; 3=active movement against gravity; 4=active movement against gravity and resistance; and 5=normal muscle strength. The total score ranges from 0 (for quadriplegia) to 60 points (for preserved

muscle strength), including shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and dorsiflexion of the ankle movements, all scored bilaterally. A score below 48 is conclusive for muscle weakness acquired in the intensive care unit[11].

The 1RM test will be performed to evaluate the dynamic strength of the quadriceps muscle. Thus, an extension chair will be used (7Cinco – Pro Sport Fitness, Porto Alegre/RS, Brazil). In the sitting position, with the hips and knees at 90° flexion, the patient will be instructed to extend both knees against the resistance placed in the anterior region of the ankles until the maximum range of motion. If two repetitions are completed, the load will be increased until the patient can perform a single maximum repetition across the range of motion without postural compensations[13].

Spasticity evaluation

The modified Ashworth scale will be used to evaluate spasticity. This scale consists of an ordinal classification of 5 points for grading the resistance found during passive stretching, where 0 indicates normal muscle tone and 4 indicates a severe increase in tone, causing flexion or extension stiffness.

The patient will be placed in the supine position and the testing the lower and upper limbs. When a muscle with flexion function is tested, the joint will be positioned in maximum flexion and the extension will be performed in one second and the same process will be conducted for a muscle that performs the extension[14].

Muscle architecture and echogenicity evaluation

The assessment of muscle architecture and echogenicity will occur by acquiring ultrasound images of the medial and vastus lateralis and rectus femoris by a high-resolution ultrasound device (Vivid-i, GE, USA). Specifically, the quadriceps muscle thickness (vastus lateralis, vastus medialis, and rectus femoris), the cross-sectional area of the rectus femoris, and its echogenicity will be evaluated. To assess the thickness of the vastus lateralis and rectus femoris, the midpoint between the greater trochanter and the lateral condyle of the femur will be used as a reference point, while measurements of the vastus medialis will be performed at 25–30% of this distance, according to patient characteristics. Three images will be obtained with the ultrasound transducer longitudinally positioned on the muscle fibers of each of the knee extensor muscles to assess muscle thickness[15]. To assess the cross-sectional area and echogenicity of the rectus femoris, three images will be obtained, however, the ultrasound transducer will be positioned transversely on the rectus femoris, with the midpoint between the greater trochanter and the lateral condyle of the femur being used as a reference[16]. Finally, all images will be analyzed using the ImageJ software.

Mobility evaluation

Mobility will be assessed by the timed up and go (TUG) test. This test consists of the movement from a sitting to a standing position, walking for three meters, changing direction during gait, and the movement from a standing to a sitting position. The shorter the time to perform the test the better is the performance[17].

During the TUG test, an inertial sensor (BTS G-Walk, Kinetec, Porto Alegre, RS, Brazil) will be attached to the patient's waist, at the height of the L4-L5 spaces, using a semi-elastic band. This sensor will allow monitoring gait phases and linear accelerations in three orthogonal axes (anteroposterior, medio-lateral and vertical) using a wireless network, transmitting the signals via Bluetooth to a computer. The time required to get up, acceleration, time, and speed of rotation will be monitored as well as the time required to sit[18,19].

Degree of disability and dependence evaluation

The modified Rankin scale will be used to determine the degree of disability and dependence after a stroke. This instrument has 6 scores, where: 0=asymptomatic; 1=symptoms without disabilities; 2=mild disability; 3=moderate disability; 4=moderate to severe disability; 5=severe disability and 6=death[20].

Functional capacity and dependence will also be verified by the functional independence measure (FIM) scale. This instrument assesses the patient's performance in the sensory motor and cognitive domains and each item varies in 7 levels with the respective measurements, with level 7 meaning total independence and level 1 total dependence. In the total scale, the patient without any disability reaches a score of 126 points, and with total dependence a score of 18 points[21].

Quality of life evaluation

Quality of life will be assessed using the EuroQol-5D (EQ-5D) questionnaire. This is a generic instrument that assesses mobility, personal care, usual activities, pain/malaise, and anxiety/depression and allows to create a general index of the value of an individual's health status. The number 1 indicates the best state of health (perfect health) and 0 the worst state of health (death)[22].

Cardiorespiratory parameters evaluation

Vital signs will be checked prior to the first intervention and during the 18 sessions to assess the cardiorespiratory response and intervention safety. The following aspects will be measured: systolic and diastolic blood pressure; heart rate; and peripheral arterial oxygen saturation. Moreover, the dyspnea index will be assessed using the modified Borg effort scale and pain will be examined using the visual analog scale (VAS).

Length of hospital stay

The days between the patient's admission and hospital discharge will be counted to assess the total length of hospital stay.

Generally, the evaluations will be executed by a researcher who is blind to the interventions at three moments: at baseline, after the 10th session, and at the end of the protocols (18th session). Some particularities: the application of the Fugl-Meyer scales, MRC, modified Ashworth scale, Rankin scale, FIM, the assessment of quadriceps muscle architecture, and quality of life will be performed prior to the interventions. In the 10th session, the Fugl-Meyer scale, MRC, and the modified Ashworth scale will be reapplied and the mobility and muscle strength tests will be performed (TUG and 1RM test respectively). At the end of the protocols (18th session) all evaluations will be repeated.

Study Protocol

Intervention

Interventions will occur during the hospital phase and after discharge. During hospitalization, protocols will be performed daily, once a day. After discharge, patients from both groups will be seen at the Rehabilitation Center of Pavilhão Pereira Filho of ISCMPA, by physical therapists specialized in robotics, three times a week, on alternate days, totaling 18 sessions at the end of the protocols. Note that, resistance training with shorter protocols has been able to contribute to neural adaptation and increased muscle fiber cross-sectional area in healthy patients[23,24].

The control group (CG) will perform conventional physical therapy during the hospital phase, conducted by physical therapists at the hospital. The exercises proposed during hospitalization aim at early mobilization, tone modulation, maintenance of joint amplitudes, maintenance/gain of muscle strength, improvement of balance, and gain of functional independence. After hospital discharge, in the outpatient phase, the same group will perform an exercise protocol according to the objectives established by the Guidelines for Adult Stroke Rehabilitation and Recovery[25]. Knee and hip flexion and extension movements will be worked on; hip adduction and abduction; respecting the articular physiology of each joint; weight transfer in the sitting position and in orthostasis and associated with trunk control movements; mini-squat and gait training. In the end, global stretching lower limbs will be conducted. Outpatient care will last 30 minutes and three series with 10 repetitions for each exercise will be performed. A progression to four series will be established from the 10th session, as well as a maximum therapy time of 40 minutes. The main parameters for exercise progression during rehabilitation are based on training with repetitions, gradually progressive task difficulty and functional practice. Finally—to make the conventional physical therapy protocol as similar as possible to that performed by the intervention group (IG) with the Erigo® device—no upper limb exercise will be performed with the CG patients.

The intervention group (IG) will perform robotic rehabilitation in the hospital phase, replacing the conventional physical therapy session conducted by physical therapists in hospital as well as after discharge. Robotic rehabilitation performed using the Erigo® device (Hocoma, Volketswil, Switzerland) provides orthostasis assisted by an orthostatic board, passive and assisted movement of the legs, in addition to neuromuscular electrical stimulation (NMES) of the quadriceps and hamstring muscles simultaneously with the mobilization of the legs. The NMES will be applied using self-adhesive electrodes size 7.5x13 (model CF7515, Arktus, São Paulo, SP, Brazil), with the following parameters: 50Hz frequency, 500μs pulse width, three seconds of ramp and current intensity according to the patient's tolerance, as long as the muscle contraction is visible[26,27].

The rehabilitation protocol performed using the Erigo® device will be based on the overload principle[28] as proposed below:

1st session: Initially the orthostatic board will be tilted until reaching 30º. If there is no hemodynamic decompensation, the inclination will be increased to 80º and the patient will remain in this position for 15 to 20 minutes, not exceeding the 500-step mark until the end of the therapy. The robot will perform the hip and knee flexion/extension movements at a cadence of 16–20 steps/minute. The driving force will be between 100–80%. For the remaining sessions, the patient will be

vertical and the mobilization of the lower limbs associated with NMES will begin immediately. The return to the starting position will have a progression similar to the initial one.

2nd to 4th session: If the patient is adapted to the inclination of the board when it reaches 90º the robot will perform the flexion/extension movements of the hip and knee respectively for 30 minutes. Cadence: 20–24 steps/minutes; driving force 80–60%.

5th to 7th session: At 90º angle; 30-minute session; cadence 24–28 steps/minutes; driving force 60–40% by the end of the protocol.

8th to 10th session: At 90º angle; 40-minute session; cadence 28–32 steps/minutes.

11th to 13th session: At 90º angle; 40-minute session; cadence 32–36 steps/minutes.

14th to 18th session: At 90º angle; 40-minute session; cadence 36–40 steps/minutes. The 18th session will be performed with a driving force of 40%.

Vital signs will be continuously monitored during robotic rehabilitation. Hemodynamic decompensation (systolic pressure with reduction >20mmHg and diastolic pressure >10mmHg or heart rate with elevation >30bpm from baseline), a significant fall in peripheral arterial oxygen saturation, tachypnea, ventilatory effort, sweating, malaise reported by the patient will be considered criteria for the interruption of training. If, in the second subsequent session of the protocol, the patient does not tolerate the intervention again or shows hemodynamic instability, he/she will be excluded from the study. The group composition flowchart, assessment, and intervention procedures are shown in Figure 1.

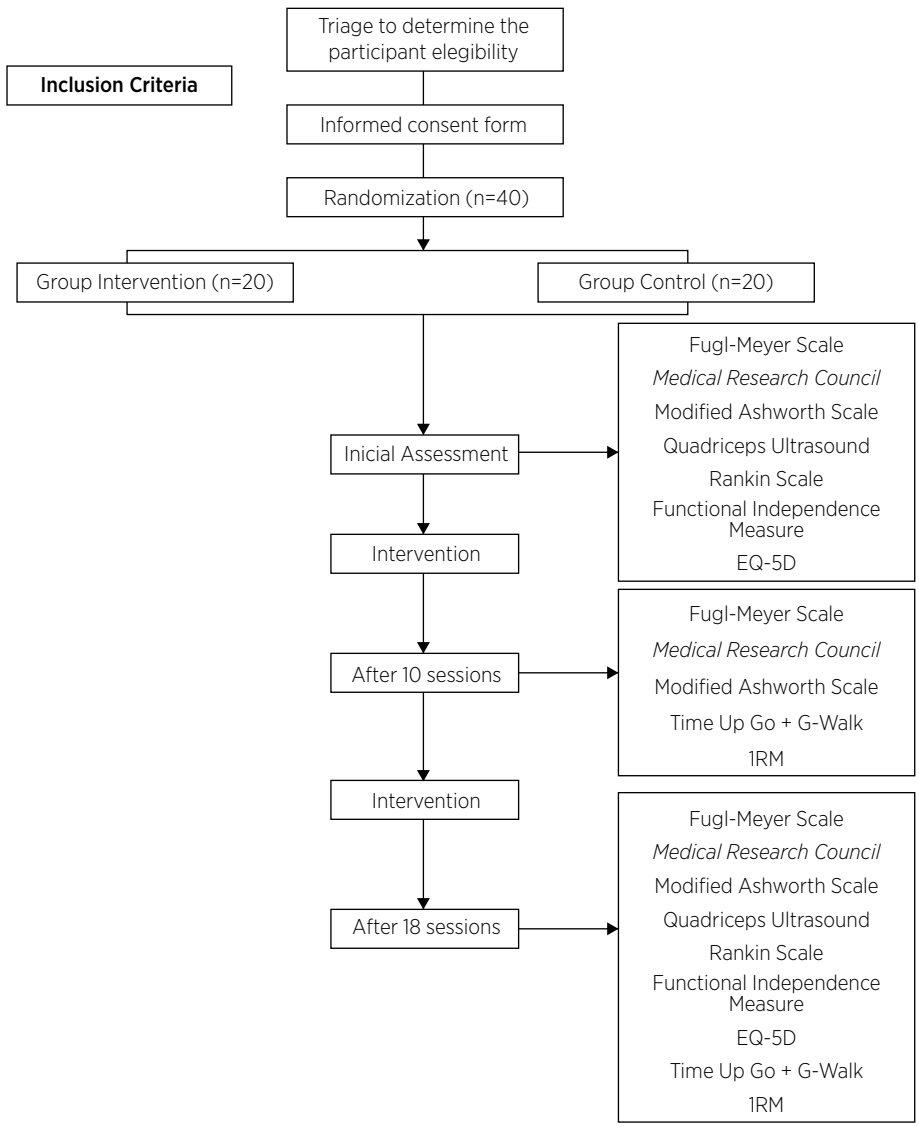

Figure1. Flowchart of groups composition, evaluations and intervention

To ensure adherence to treatment, all patients need to perform at least 15 out of the 18 robotic rehabilitation or conventional physical therapy sessions provided by the protocol. Moreover, if any major adverse effect occurs as a result of the interventions proposed in this protocol, the researchers will provide medical assistance to the patient and the protocol will be reviewed. Finally, patients included in the study will not receive motor rehabilitation from another health professional as occupational therapist or speech therapist during the protocol.

Data analysis

The sample was calculated using the Gpower® software version 3.1 and was based on a study by Calabrò et al.[9] that evaluated the effect of robotic rehabilitation using the Erigo® device in stroke patients. The muscle strength assessed by the MRC scale was adopted as the outcome to estimate the sample size, using a mean difference between the control and intervention groups of +1 and +2 respectively, the standard deviation of ±1, alpha error of 5% and 80% power. Thus, the sample size was estimated to be 17 patients per group. Predicting losses, 20 patients will be recruited per group.

After data collection, for data analysis, generalized estimating equation (GEE) will be used to analyze the effect of the intervention between the groups. The level of significance adopted will be 5% ($p<0.05$).

All data collected during the study will be stored on a computer by one of the team's researchers and copies will be made daily to a second device for security reasons. Patient identification data will be kept confidential by identifier numbers and the results of the study will be disclosed only at events and in scientific journals.

DISCUSSION

This protocol of a randomized clinical trial may bring a new perspective on the rehabilitation of patients with subacute stroke, demonstrating whether robotic rehabilitation using the Erigo® device has positive effects on functioning and whether robotic rehabilitation is better than conventional physical therapy for this population.

Besides, this study intends to establish a reproducible protocol for the rehabilitation of stroke patients in the Erigo® device, establishing a progression of steps and muscle activation by the patient, following the principle of work overload.

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