Evaluation of Electrical Activity of the Tibialis Anterior Muscle and Balance in Individuals with Hemiparesis Stemming from a Stroke Submitted to Central and Peripheral Stimulation – Protocol for a Randomized, Double-Blind, Clinical Trial

(Title is too length)

Abstract

Concomitant transcranial direct current stimulation (tDCS) is suggested to enhance the functional effects of other physical rehabilitation methods in individuals with motor impairment stemming from a chronic cerebrovascular disease. Thus, the primary aim of the proposed study is to analyze the electrical activity of the tibialis anterior (TA) muscle of the paretic limb in stroke survivors following an intervention involving the combination of tDCS over the motor cortex and peripheral electrical stimulation (PES) administered over the paretic TA. The secondary objective is to analyze the effect on dynamic balance. **Methods:** Thirty-six adult stroke survivors will be randomized into three groups: 1) Active PES + sham tDCS; 2) active PES + active tDCS and 3) sham PES + active tDCS. TDCS will be administered with the anode over the primary motor cortex (M1) of the damaged hemisphere and the cathode over M1 of the undamaged hemisphere with a current of 2 mA for 20 minutes. For sham tDCS, the equipment will be switched on for only 20 seconds. PES will be administered to the paretic TA at 50 Hz for 30 minutes. Evaluations: the median frequency and root mean square (RMS) of the paretic TA will be analyzed using electromyography (EMG) and balance will be evaluated using the Mini-Balance Evaluation System (Mini-BESTest) at baseline (pre-intervention), after 10 treatment sessions at a frequency of five times a week for two weeks (post-intervention) and 30 days after the end of the interventions (follow up). Data analysis: The Shapiro-Wilk test will be used to determine the normality of the data (EMG and Mini-BesTest). Parametric data will be compared using repeated-measures ANOVA. Nonparametric data will be compared using the Kruskal-Wallis test. Effect sizes will also be calculated. **Discussion:** PES has proven to facilitate the conduction of sensory-motor afferences to the cerebral cortex in stroke survivors. Combining PES with tDCS, which has a direct effect on increasing cortical excitability, could favor motor acquisition and neuronal plasticity in this population.

Key words: hemiparesis, tibialis anterior, transcranial direct current stimulation, electromyography, balance. (Keywords – Should be in alphabetical order

Introduction

The physiopathology of cerebrovascular accident (stroke) is a governed by the leakage of blood or restricted blood flow in a given area of the brain. According to data from the World Health Organization, stroke is the third major cause of morbidity, mortality and disability adjusted years of life in the world.[1] In Brazil, it is the leading cause of death and acquired physical disability, with an annual incidence of 108 cases per 100 thousand inhabitatants.[2]

Difficulty performing hip flexion, knee flexion and dorsiflexion of the foot are among the disabilities commonly found in stroke survivors. In some individuals, the ankle remains in the extended position, which is denominated equinus foot, characterized by hypertonia of the gastrocnemius and soleus (triceps surae) muscles and a reduction in or absence of strength in the tibialis anterior (TA) muscle.[3] This situation affects the adequate support of the feet on the ground, which makes the individual distribute his/her weight more to the non-paretic side as a compensatory mechanism.[4] Consequently, the individual experiences a reduction in postural control and gait velocity, leading to greater insecurity, a risk of falls and functional limitations.[4]

To minimize these dysfunctions, a large number of clinical trials have been developed to demonstrate the effect of peripheral electrical stimulation (PES) in this population (Howlett et al. 2015).[5] Bakhtiary et al. (2008) (Kindly check the manuscript reference format) combined PES with exercises based on the Bobath concept in 40 stroke survivors and found an increase in dorisflexion range of motion, a reduction in spasticity of the plantar flexors and a gain in TA muscle strength.[6] Cheng et al. (2010) used PES on the TA of 15 individuals with hemiparesis stemming from a stroke combined with active contraction of the dorsiflexors in the standing position on a balance platform for 30 minutes, followed by 15 minutes of gait training focused on ankle control, resulting in a reduction in dynamic spasticity of the plantar flexors, an increase in dorisflexor strength and improved gait symmetry.[7] Kyunghoon et al. (2015) combined PES with ankle strength and proprioception training or ankle stretching and proprioception training in 11 individuals with hemiparesis stemming from a stroke and found that the former combination resulted in positive effects on balance performance.[8]

PES is performed using equipment that emits low-level electricity applied to the skin, which promotes the depolarization of muscle fibers (for a gain in muscle strength) and the relaxation of spastic muscles.[9] However, divergent opinions are found in the literature on the ideal parameters (duration/number of applications, pulse, intensity and

frequency) for neurological diseases and better results are achieved when combined with other forms of rehabilitation.

In this context, researchers have proposed investigating the combination of PES and other forms of electrical stimulation to enhance its effects, such as transcranial direct current stimulation (tDCS). Kwon et al. (2011)[10] evaluated the activity of the primary motor cortex (M1) using magnetic resonance imaging in two healthy individuals during a session of anodal tDCS over M1 combined with PES of the wrist extensors and found an increase in M1 activity. Rizzo et al. (2014)[11] investigated the motor evoked potential in 10 young healthy individuals after 10, 20, 30 and 60 min of anodal or cathodal tDCS over M1 combined with repetitive PES over the left median nerve and found that anodal stimulation + repetitive PES led to an increase in the motor evoked potential up to 60 minutes after stimulation. In a study involving 20 stroke survivors in the subacute phase, Sattler et al. (2015)[12] evaluated the effect of anodal tDCS over M1 combined with PES over the radial nerve for five consecutive weeks and found a significant increase in motor function of the hand up to one month after treatment. However, Fruhauf et al. (2018)[13] evaluated the immediate effect of tDCS combined with PES on electrical activity of the paretic TA muscle and balance in 30 stroke survivors and found no effect after the administration of the two techniques combined. The researchers suggest that this may have occurred because only a single session was used, implying that longer treatment with the combination of the techniques could achieve different results. No clinical studies were found investigating the combination of PES and tDCS for more than one treatment session with the aim of assessing electrical activity of the TA muscle and functional balance in stroke survivors.

TDCS consists of a low-intensity electrical current generally administered over the scalp using two electrodes of different polarity (anode and cathode). The current is able to penetrate the skull and produce modulating effects on the neural membrane, either increasing (anodal stimulation) or diminishing (cathodal stimulation) cortical excitability.[14]

When combined with other forms of treatment, tDCS has been demonstrated to enhance the effects of physical therapy.[15] Dutta et al. (2014)[16] studied the effect of tDCS over the primary motor cortex and cerebellum combined with ankle training involving biofeedback in healthy individuals to improve myoelectrical control of the TA muscles and found that anodal stimulation over M1 resulted in the optimization in terms of the onset and end of electrical activity in the muscles. Madhavan et al. (2011)[17] found an

increase in motor evoked potential for 15 minutes and immediately after the end of ankle dorsiflexion training combined with tDCS over M1 in stroke victims. Sohn et al. (2013)[18] investigated the effect of tDCS over the damaged M1 in 11 individuals with hemiparesis and found significant increases in quadriceps strength and static postural stability.

These interactions (central and peripheral stimulation) may translate to benefits in function, especially in cases o neurological disorders, as tDCS enhances cortical excitability, facilitating ascending sensory-motor information triggered by the use of PES. Therefore, the present protocol proposes the investigation of the effects of tDCS combined with PES in individuals with hemiparesis stemming from a stroke on electrical activity of the TA muscle and balance, since these factors are important to functional independence.

Aims and Objectives??????

Methods

Study design

A randomized, sham-controlled, double-blind, longitudinal, clinical trial is proposed.

The primary outcome of this study will be the electrical activity in the TA muscle, determined using eletromyography (EMG). Evaluations will be performed on three occasions: 1) baseline (pre-intervention) 2), after 10 treatment sessions (post-intervention) and 3) 30 days after the end of the sessions (follow up). The secondary outcome will be balance, determined using Mini-Balance Evaluation System (Mini-BESTest). The participants will be recruited from the physical therapy clinics of University Nove de Julho, São Paulo, Brazil. The flow of the study is shown in Figure 1.

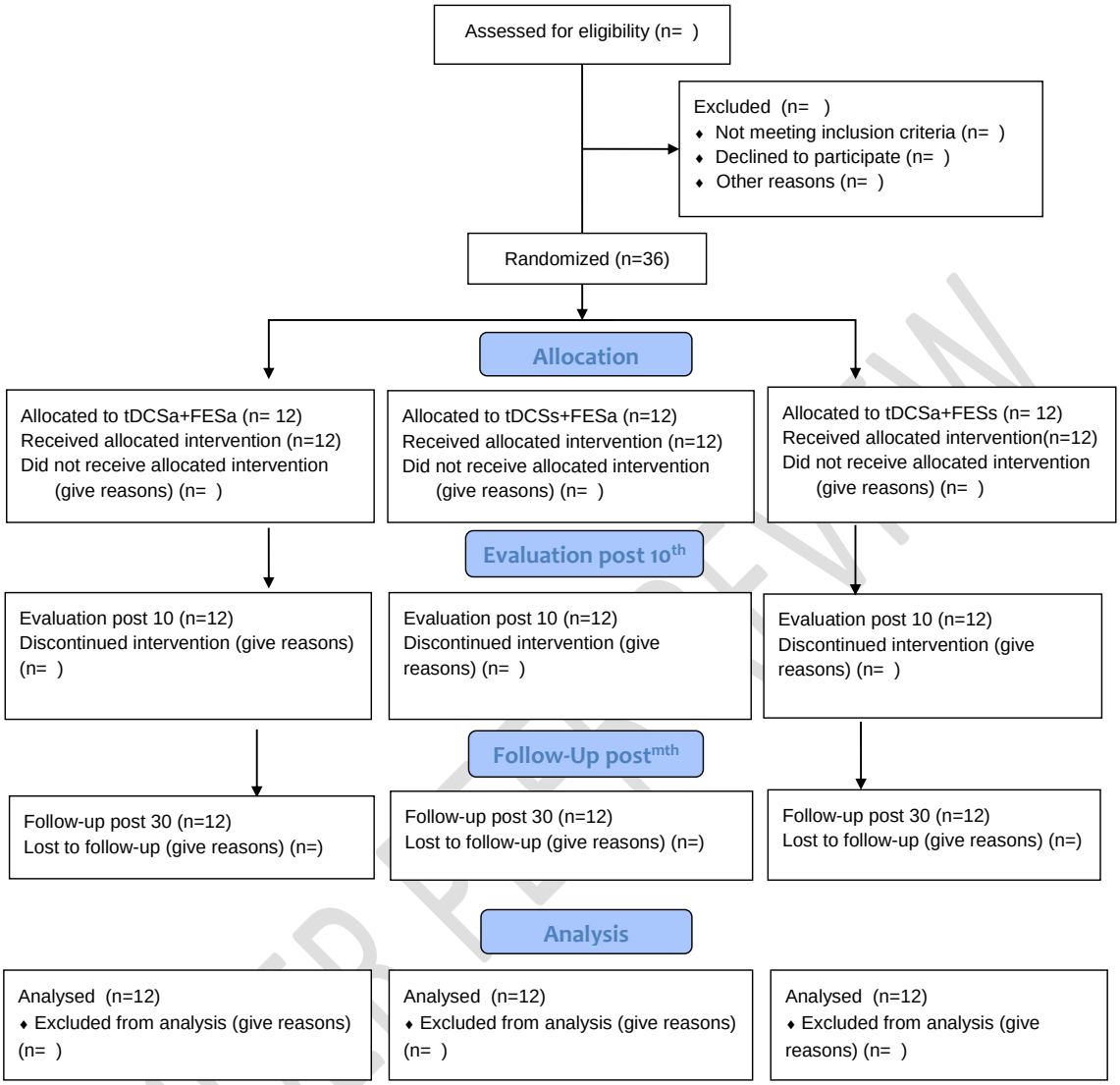

Figure 1. Flowchart of study.

Eligibility criteria

The following are the inclusion criteria: hemiparesis stemming from a stroke in the chronic stage;[2] TA muscle weakness (> 1 and < 5 on the Medical Research Council scale);[19] adults (> 20 years of age) with independent gait (with or without a gait assistance device); agreement to participate through the signing of a statement of informed consent. The following are the exclusion criteria: positive cutoff point for cognitive impairment on the Mini Mental State Examination (less than 11 points; corrected for schooling);[20] diagnosis of severe depression (Beck Depression

Inventory);[21] active ankle mobility less than 5 degrees (determined using a goniometer);[22] muscle stiffness during flexion or extension (Ashworth Scale);[23] need for the use of orthopedic insoles or rigid braces; use of botulinum toxin in the lower limbs; severe visual impairment (confirmed by ophthalmological exams); contraindication for tDCS (history of seizures, tumors at stimulation site; metal implants in skull [all confirmed by medical exams]); skin lesion at application site of tDCS or PES (visual inspection by therapist); anesthesia or hyperesthesia at central or peripheral stimulation site (physical evaluation of surface sensitivity using a esthesiometer); diagnosis of deep vein thrombosis (confirmed by medical exam); diagnosis of degenerative disease or polyneuropathy (confirmed by medical exam); undergoing physical therapy or alternative therapy during the development of the study or in the one-month period after the 10 treatment sessions.

Sample size

The sample size was calculated using the G*Power program. Based on the results of a study by Sabut et al. (Surface EMG Analysis of Tibialis Anterior Muscle in Walking with PES in Stroke Subjects),[24] the calculation was performed considering mean and standard deviation root mean square (RMS) values for the experimental group before and after PES (60 ± 6 and 110 ± 11, respectively), $\alpha = 0.05$, $\beta = 0.2$ (80% power) and a 0.94 effect size. Twelve individuals were determined for each group (total sample: 36 individuals).

Randomization

The allocation of the 36 participants (12 per group) will be randomized and counterbalanced using a randomization table in Excel™ with codes for the combinations of the two central (active or sham) and two peripheral (active or sham) stimulations.[13] A researcher not involved in the evaluations or treatment will be responsible for the randomized allocation of the participants to the three groups:

1- Active bilateral tDCS (anode over damaged hemisphere and cathode over undamaged hemisphere) + active PES over paretic TA;
2- Sham bilateral tDCS (anode over damaged hemisphere and cathode over undamaged hemisphere) + active PES over paretic TA;

3- Active bilateral tDCS (anode over damaged hemisphere and cathode over undamaged hemisphere) + sham PES over paretic TA.

Blinding

The NeuroConn DC-STIMULATOR PLUS device has settings that enable the selection of the active stimulation mode or sham mode by entering codes. A researcher not involved in the treatment or evaluations will program the equipment with the code to which the patient was allocated. The type of stimulation (active or sham) will not be perceptible by visual cues or the external functioning of the device. Therefore, neither the researcher who will place the equipment on the patient nor the patient will know which treatment he/she is receiving (double-blind study).

Data collection, management and analysis

Procedure should be brief?????

For all evaluation procedures, the participants will be seated on a chair with a backrest, with knees flexed at 90 degrees and ankle in the neutral position.

Electromyography of tibialis anterior muscle

The EMG data of TA muscle activity will be analyzed by the amplitude/power of the signal (RMS) and muscle fiber recruitment rate (median frequency) captured using the EMG SYSTEM®, consisting of an A/D converter with 16 bits of resolution, six channels and data transmission. The EMG signals will be pre-amplified with a gain of 1000 fold, a common rejection mode ratio > 100 dB and filtered using a 20-450 Hz bandpass filter, with a sampling frequency of 1 kHz. The data will subsequently be coded using routines developed in MATLAB® version R2010a (The MathWorks Inc., Natick, Massachusetts, USA).

Two disposable surface electrodes (Ag/AgCl – Medical Trace®) measuring 10 mm in diameter will be positioned over the skin (previously cleaned with 70% alcohol) in the region of the TA, following the guidelines of the Surface Electromyography for the Noninvasive Assessment of Muscles (SENIAM).[25] For each reading, the

patient will perform three maximum voluntary isometric contractions of the TA (maximum active dorsiflexion) for 10 seconds following a verbal command, followed by rest for 2-3 minutes between each reading. Next, the participant will perform five consecutive concentric contractions (isotonic) of the TA three times, with 2-3 minutes of rest between each reading.[13]

No previous study has been conducted to determine the reliability of this tool for the population of stroke survivors, but this instrument has demonstrated solid, effective results in the investigation of muscle actions in this group of patients.[26,27].

Mini-Balance Evaluation System (Mini-BESTest)

Functional balance will be evaluated using the Mini-BESTest, which consists of 14 tasks distributed among four domains: (1) anticipatory postural adjustments (transition from sitting to standing position; standing on the tips of the toes; one-legged stance); (2) postural responses (four different direction of body movement: anterior, posterior and side-to-side); (3) sensory orientation (feet together on a stable surface with eyes open; feet together on an unstable surface with eyes open; leaning with eyes closed) and (4) gait stability (walking with change in velocity; horizontal movement of the head; around obstacles; turning on one's own axes; and with and without a cognitive dual task).[28]

Each item is scored on a four-point scale from zero (worst performance) to three (best performance). The maximum score is 28 points.[28] This instrument has high reliability for the evaluation of balance in stroke survivors (ICC > 0.90).[29]

Determination of potential confounding factors

Depressive symptoms

Depressive symptoms will be evaluated and graded with regard to severity using the Beck Depression Inventory (BDI),[30] which is a self-administered questionnaire composed of 21 items. Each item is scored from 0 to 3 points. The total ranges from 0 to 63 points and is interpreted as follows: 0 to 10 indicates the absence of depression; 11 to 18 = mild depression; 19 to 29 = moderate depression; and 30 to 63 = severe depression. The BDI score will be determined on three occasions (pre-intervention, post-intervention and 30-day follow up) and used as a covariant to determine whether

motor recovery is independent of possible mood-related effects.[31] The reliability of the BDI is 0.89 and this measure has been used in studies that have shown good clinical results.[32]

Evaluation for characterization of sample

Fugl-Meyer Scale

The measures proposed on the Fugl-Meyer Scale are based on the neurological examination and sensory-motor activity of the upper and lower limbs to determine selective activity and synergic patterns in patients who have suffered a stroke. This is an accumulative numeric scoring system used to evaluate range of motion, pain, sensitivity, upper and lower limb motor function, balance, coordination and velocity, totaling 226 points.[33] A three-point ordinal scale is used for each item: 0 – not performed; 1 – partially performed; and 2 – fully performed. The scale has a total of 100 points for normal motor function, in which the maximum score is 66 for the upper limbs and 34 for the lower limbs.[33] The score is interpreted as follows: < 50 points = severe motor impairment; 50-84 = marked impairment; 85-95 = moderate impairment; and 96-99 = mild impairment. The Fugl-Meyer Scale will be used in this study for the characterization of the individuals considering demographic aspects, degree of global motor impairment and specific motor impairment of the lower limbs. In the literature, this scale has high reliability (ICC = 0.99 and 0.98, respectively) for the evaluation of stroke survivors.[34]

Interventions

For both interventions, the patient will be seated on a chair with a backrest, knees flexed at 90° and ankle in the neutral position.[13] Treatment will consist of 10 sessions (five per week for two weeks). PES will last 30 minutes per session,[5] the first 20 minutes of which will be combined with tDCS.[13]

Transcranial direct current stimulation

The one-channel unipolar DC Stimulation plus (neuroConn) will be used. Stimulation will be administered through two silicone/carbon electrodes 5 x 5 cm

covered in sponge soaked in saline solution. The anode will be positioned over the primary motor cortex of the damaged hemisphere (C1 or C2) and the cathode will be positioned over the primary motor cortex of the undamaged hemisphere (C1 or C2) – both at a distance of 2 cm from Cz based on the map of the 10-20 International Electroencephalogram System.[35] Central stimulation with tDCS will occur concomitantly to peripheral stimulation (first 20 minutes of PES) with a current of 2 mA.[36]

Sham stimulation will involve the same procedures as active stimulation, but the stimulator will only be switched on for the first 20 seconds, after which the current will be reduced to zero. All patients will be informed that they may feel a mild initial tingling that may disappear or may continue throughout the 30 minutes of treatment. This is considered a valid control procedure for the use of tDCS.[37]

Determination of potential side effects

Possible adverse effects stemming from noninvasive brain stimulation will be determined using the TDCS – Side Effects Questionnaire (version translated into Portuguese) after each session with tDCS.[38]

Peripheral electrical stimulation

The two-channel QUARK® FES VIF 995 DUAL will be used for PES. Two self-adhesive rubber electrodes measuring 5 x 9 cm will be positioned on the motor point and belly of the paretic TA muscle.[13] PES will be performed with a pulse width of 250 µs and frequency of 50 Hz. The intensity will be increased until reaching the motor threshold (20-30% of maximum voluntary contraction).[13] The stimulation cycles will be 1:2 (six seconds on and 12 seconds off)[13] combined with active contraction of the TA every six seconds for 30 minutes.[13] Sham stimulation will involve the same procedures as active PES, but the electrodes will be positioned in the tibial region (bone portion).[39]

Statistical analysis

Descriptive data, characteristics of the sample (gender, age, type of stroke [ischemic or hemorrhagic], damaged hemisphere [right or left], time elapsed since the stroke event, Fugl-Meyer lower limb score, Beck Depression Inventory (BDI), use of controlled medications and associated comorbidities will be expressed as mean and standard deviation values or median and interquartile range.

The Shapiro-Wilk test will be used to determine the normality of the data (EMG and Mini-BesTest). Repeated-measures ANOVA will be used for the comparison parametric data and the Kruskal-Wallis will be used for nonparametric data. The effect size will also be determined for the comparison of evaluation times (pre-intervention, post-intervention and 30-day follow-up). A (P = < 0,05 will be considered indicative of statistical significance. All analyzes will be processed using the IBM SPSS program v.19.

Discussion

This article presents a detailed description of a prospective, randomized, controlled, double-blind trial designed to demonstrate the effects of the combination of transcranial direct current stimulation and functional electrical stimulation on electrical activity of the tibialis anterior muscle and postural control in individuals with hemiparesis stemming from a stroke. The results will be published and the evidence could contribute to the rehabilitation of this population.

(Discussion – should be more with relevant and recent updates)

Limitation

Recommendation???

Trial status

At the time of manuscript submission, we were recruiting patients. The study in question is expected to be completed in December 2019.

Abbreviations

BDI: Beck Depression Inventory
EMG: electromyography
Hz: Hertz
M1: primary motor cortex
Mini-BESTest: Mini-Balance Evaluation System
PES: peripheral electrical stimulation
RMS: root mean square
SENIAM: Surface Electromyography for the Non-Invasive Assessment of Muscles**.**
TA: tibialis anterior muscle
tDCS: transcranial direct current stimulation

Acknowledgments

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Availability of data and materials

Data sharing is not applicable to this article because no datasets were generated or analyzed during the present study.

Authors' contributions

FIC and AMAF designed the study. The data collection, interventions and recruitment of the participants were performed by CCS and DCA. The manuscript was prepared by FIC and AMAF, which was revised and edited by FP and JCF. All authors read and approved the final manuscript.

Trial Registration: Clinical Trials: NCT03008720.

Ethics approval and consent to participate

This protocol received approval from the Human Research Ethics Committee of University Nove de Julho, São Paulo, Brazil (certificate number: 2.015.168) in compliance with Resolution 466/12 of the Brazilian National Board of Health. Written informed consent will be obtained from each participant.

Participating volunteers must accept the study consent form (attached document), which ensures the confidentiality of data, free access to the final data, explanations of any nature related to treatment and compensation for those suffering from participation in trials. The results of this study will be published in a journal of interest in the field of physical therapy and rehabilitation.

Ethics approval: This protocol received approval from the Human Research Ethics Committee of University Nove de Julho, São Paulo, Brazil (certificate number: 2.015.168) in compliance with Resolution 466/12 of the Brazilian National Board of Health.

Competing interests

The authors declare that they have no competing interests.

References

1. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; pp. 2197-223.
2. Bensenor IM, et al. Prevalence of stroke and associated disability in Brazil: National Health Survey – 2013. Arq. Neuro-Psiquiatr. vol.73 no.9 São Paulo Sept. 2015.
3. Andrews AW, Bohannon RW. Distribution of muscle strength impairments following stroke. Clin. Rehabil. 2000; pp. 14:79.
4. Azevedo ERFBM, Macedo LS, Paraízo MFN, Oberg TD, Lima NMFV, Cacho EWA. Correlação do déficit de equilíbrio, comprometimento motor e independência funcional em indivíduos hemiparéticos crônicos. Acta Fisiátrica. 2008;15(4):225-8.
5. Howlett OA, Lannin NA, Ada L, Mckinstry C. Functional electrical stimulation improves activity after stroke: a systematic review with meta-analysis. Arch. Phys. Med. Rehabil. 2015; pp. 934-43.

6. Bakhtiary AH, Fatemy E. Does electrical stimulation reduce spasticity after stroke? A randomized controlled study. Clin. Rehabil. 2008; pp. 418-25.
7. Cheng JS, Yang YR, Cheng SJ, Lin PY, Wang RY. Effects of combining electricstimulation with active ankle dorsiflexion while stadng on a rocker board: a pilot study for subjects with spastic foot after stroke. Arch. Phys. Med. Rehabil. 2010; pp. 505-12.
8. Kyunghoon, Lee S, Donghoon, Sik K. The effects of ankle joint muscle strengthening, and proprioceptive exercise programs accompanied by functional electrical stimulation on stroke patients'balance. J. Phys. Ther. Sci. 2015; pp. 2971–2975.
9. Rushton D.N. Functional Electrical Stimulation and rehabilitation- an hypothesis. Medical Engineering & Physics. 2003; pp 75–78.
10. Kwon et al. Cortical Activation by Transcranial Direct Current Stimulation and Functional Electrical Stimulation in Normal Subjects: 2 Case Studies. J Kor Soc Phys Ther 2011;23(1):77-82.
11. Rizzo V, Terranova C, Crupi D, Sant'angelo A, Girlanda P, Quartarone A. Increased transcranial direct current stimulation after effects during concurrent peripheral electrical nervestimulation. Brain Stimul. 2014; pp.113-211.
12. Sattler, V. *et al.* (2015) 'Anodal tDCS Combined With Radial Nerve Stimulation Promotes Hand Motor Recovery in the Acute Phase After Ischemic Stroke', *Neurorehabilitation and Neural Repair*, 29(8), pp. 743–754.
13. Fruhauf AMA, Politti F, Dal Corso S, et al. Immediate effect of transcranial direct current stimulation combined with functional electrical stimulation on activity of the tibialis anterior muscle and balance of individuals with hemiparesis stemming from a stroke. *J Phys Ther Sci*. 2017;29(12):2138-2146.
14. Bikson M, Datta A, Rahman A, Scaturro J. Electrode montages for tDCS and weak transcranial electrical stimulation: Role of "return" electrode's position and size. Clin. Neurophysiol. 2010; 121 (12): 1976–1978.
15. Holgado, Darías et al. The effects of transcranial direct current stimulation on objective and subjective indexes of exercise performance: A systematic

review and meta-analysis. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation.2019; 12(2): 242 – 250.

16. Dutta A, Paulus W & Nitsche MA. Facilitating myoelectric-control with transcranial direct current stimulation: a preliminary study in healthy humans. Journal of NeuroEngineering and Rehabilitation. 2014; pp. 11:13.
17. Madhavan S, Weber KA, Stinear JW. Non-invasive brain stimulation enhances Wne motor control of the hemiparetic ankle: implications for rehabilitation. Exp. Brain Res. 2011; pp. 9–17.
18. Sohn MK, Sung JJ, Yeong W. Effect of Transcranial Direct Current Stimulation on Postural Stability and Lower Extremity Strength in Hemiplegic Stroke Patients. Ann. Rehabil. Med. 2013; pp. 759-765.
19. Hermans G, et al. Interobserver agreement of Medical Research Council sumscore and handgrip strength in the intensive care unit. Muscle Nerve. 2012;45(1):18-25.
20. Maheshwari SG, IqbaL M, Hashmi SFA, Devrajani B. Stroke patients; assessment of cognitive impairment in. Professional Med. J. 2015; pp. 541-545.
21. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J . An inventory for measuring depression. Arch. Gen. Psychiatry. 1961; 4: 561–71.
22. Madhavan S, Weber KA, Stinear JW. Non-invasive brain stimulation enhances Wne motor control of the hemiparetic ankle: implications for rehabilitation. Exp. Brain Res. 2011; pp. 9–17.
23. Ashword B. Preliminary trial of carisoprodol in multiplesclerosis. Practitioner. 1964; pp. 540–2.
24. Sabut, R. Kumar, P.K. Lenka, M.M. Surface EMG Analysis of Tibialis Anterior Muscle in Walking with FES in Stroke Subjects. Conf Proc IEEE Eng Med Biol Soc.2010: pp. 5839-42.
25. Hermens HJ, Freriks B, Disselhorst- Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. J. Electromyography and Kinesiology.2000; pp. 361–74.
26. Suhaimi, R. et al. Analysis of EMG-based Muscles Activity for Stroke Rehabilitation. 2014 2nd International Conference on Electronic Design, ICED 2014. 10.1109/ICED.2014.7015792.

27. Tania, FC. et al. Electromyographic analysis of spastic muscles in hemiparetic patients before and after physical therapy intervention. Ter Man. 2012; 10(48):148-153.
28. Charlotte SLT, Lin RL, Raymond CK, Chung MYC. Psychometric Properties of the Mini-Balance Evaluation Systems Test (Mini-BESTest) in Community-Dwelling Individuals with Chronic Stroke. *Phys Ther* 2013; 93 (8): 1102-1115.
29. Carla B, Lívia CM , Fátima RP. Electromyographic analysis of spastic muscles in hemiparetic patients before and after physical therapy intervention. Ter Man. 2012; 10(48):148-153.
30. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J . An inventory for measuring depression. Arch. Gen. Psychiatry. 1961; 4: 561–7.
31. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-613.
32. An TG, Kim SH, Kim KU. Effect of transcranial direct current stimulation of stroke 528 patients on depression and quality of life. J Phys Ther Sci. 2017;29(3):505-507.
33. Fugl-meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient: A method for evaluation of physical performance. Scand. J. Rehab. Med. 1975; pp. 13-31.
34. MAKI, T. et al. Estudo de confiabilidade da aplicação da escala de fugl-meyer no Brasil. Rev. bras. fisioter. Vol. 10, No. 2 (2006), 177-183.
35. Edwin HFA, Tjitske AB. Transcranial Direct Current Stimulation of the Leg Motor Cortex Enhances Coordinated Motor Output During Walking With a Large Inter-Individual Variability. Brain Stimulation 9 (2016) 182–190.
36. Adeyemo BO, Simis M, Macea DD, Fregni F. Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke.Front.Psychiatry. 2012; pp. 3:88.
37. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. Clinical Neurophisiology. 2006; pp.1623–1629.

38. Xu J, Fregni F,Brody AL, Rahman AS. Transcranial direct current stimulation reduces negative affect but not cigarette craving in overnight abstinent smokers.Front Psychiatry.2013;20:4-12.

39. Ambrosini E, Ferrante S, Pedrocchi A, Ferrigno G, Molteni F. Cycling induced by electrical stimulation improves motor recovery in post-acute hemiparetic patients: a randomized controlled trial. 2011; pp. 1068-73.