Evaluation of the immediate effects of manual acupuncture on brachial bicip muscle function in healthy individuals and poststroke patients: a study protocol of a parallel-group randomized clinical trial

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BACKGROUND: Stroke is a morbid entity in Chinese medicine recognized for over 2000 years with sensory-motor impairments reported by several classical authors. However, the majority of controlled clinical trials of acupuncture in the treatment of poststroke recovery failed to obtain significant long-term results on functional recovery. Moreover, contradictory results have been obtained regarding the immediate effects of acupuncture stimulation on the electrical activity of human skeletal muscles as observed using surface electromyography. These results raise the question of whether acupuncture has any effect on the neuromuscular level. This study aims to evaluate the immediate effects of manual acupoint stimulation on the electrical activity and strength of the biceps brachii of healthy individuals and patients with chronic hypertonic hemiparesis.

METHODS AND DESIGN: The study proposes a single-blinded randomized clinical trial with four parallel groups. Healthy subjects and poststroke patients with chronic spastic hemiparesis will be submitted to a single acupuncture intervention puncturing either Ouchi (LI11) or Tianquan (PC2). The immediate effects on muscle function will be assessed by surface electromyography and isometric force of the biceps brachii muscle as the primary outcome. Secondary outcomes comprise the frequency of patterns in each group, as well as the frequency distribution of manifestations.

DISCUSSION: The proposed study design includes some improvements on common methodological issues on clinical trials with an integrative design. This study design is expected to provide new insights on the neuromuscular effects of acupuncture stimulation in healthy subjects and poststroke patients.

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The World Health Organization estimates that deaths related to cardiovascular diseases will increase to 24 million in 2030. It is estimated that 10.6% of all ischemic strokes affect the Brazilian population aged between 15 and 40 years[1,2]. Although advances were achieved in primary and secondary preventive medicine, annually more than 70% of all strokes are first-ever events. Altogether, these data reinforce the importance of management of risk factors for stroke as well as the research on new interventions for rehabilitation for minimization of both recovery time and neurologic impairments and maximization of functional independence of stroke survivors[4,5].

Stroke is a morbid entity in traditional Chinese medicine (TCM) recognized for at least 2,000 years[6] with sensory-motor impairments reported by several classical authors. In TCM, acupuncture and herbal compounds are commonly reported interventions that depend on underlying patterns[7]. The advances of scientific methods and the worldwide effort for development of an integrative, personalized medicine, motivate researchers to investigate the efficacy of acupuncture for stroke-related functional deficits. However, the majority of controlled clinical trials of acupuncture on poststroke patients failed to obtain significant long-term results on functional recovery[8]. These results raise the question whether acupuncture has any effect on a neuromuscular level.

Functional deficits in chronic, poststroke patients have been described as the expression of abnormal synergies and co-contraction of agonist and antagonist muscles, especially in the upper and lower extremities. It has been found that those deficits were due to improper motor unit (MU) recruitment and imbalance of strength between agonist and antagonist muscles. Such an argument suggests that assessment of MU recruitment may add information on the effects of interventions aiming to improve agonist motor function in poststroke patients[9].

Surface electromyography (sEMG) has been used to evaluate muscle activity in both healthy and morbid conditions. It is a noninvasive technique that assesses the amount and duration of muscle activity, as well as strategies of neural recruitment. Among several parameters of sEMG quantification, the root mean squared (RMS) value has been the most used time-domain parameter since it better reflects the relationship between muscle tension and the corresponding gross MU recruitment[10,11]. Hence, it can be used to monitor changes in myoelectric activity due to rehabilitation interventions.

Contradictory results were obtained about the immediate effects of acupuncture stimulation on the electrical activity of human skeletal muscles as observed with sEMG. Toma et al[12] analyzed the sEMG signals of the flexor digitorum superficialis, flexor digitorum profundus, and semitendinous (n = 17; 20 to 38 years). Interventions comprised of perpendicular needle insertion into these muscles during 15 min but no acupoint was specified. A significant increase in sEMG responses was observed during maximal knee flexion but no significant differences were observed for the handgrip sEMG values. Tough[13] analyzed sEMG activity of the common wrist extensor muscles (n = 35; 18 to 70 years). Results showed that sEMG was reliable (intraclass correlation coefficient = 0.999 6), but no significant difference was observed among
protocols. Costa et al.\textsuperscript{[11]} investigated sEMG signals from the tibialis anterior muscle ($n = 15$ per group; 18 to 25 years). The effects of manual stimulation on acupoints Zusanli (ST36) and Yinlingquan (SP9) were evaluated by RMS value and maximal isometric voluntary contraction (MVIC) force estimated from sEMG and force signal, respectively. A significant reduction in RMS values was observed in both ST36 and SP9 immediately after acupuncture, but MVIC was significantly reduced only after stimulation of ST36. Moncayo et al.\textsuperscript{[15]} suggested that traditional acupuncture concepts of tonification lead to an improved function of any meridian while sedation reduces the excess. Therefore, as related to sEMG signals derived from those muscles, the signal should increase in tonification and decrease in sedation. Additionally, they claim that previous results\textsuperscript{[13]} are better explained by TCM theory than by the stimulation-reflex loop.

Currently, no study investigated the immediate effects of manual acupuncture stimulation on sEMG in poststroke patients and results with healthy subjects\textsuperscript{[15,16]} cannot be extrapolated to poststroke patients. TCM theory states that healthy subjects may present different frequency distributions of patterns compared to poststroke patients with different responses to acupuncture stimulation. From the biopsychosocial model, the structural lesion observed in poststroke patients will impose a limited control of muscle activation leading to different strategies for MU recruit-

ment. Thus, this study is justified by the seriousness of motor impairments and functional disability arising from stroke, and especially in the scientific community’s responsibility to provide and update methods for early diagnosis and treatment of these survivors. Therefore, this work proposes a study protocol for assessment of the muscle function in the upper extremity of poststroke patients with chronic spastic hemiparesis.

The aim of this study protocol is to evaluate the immediate effects of manual acupoint stimulation on both electrical activity and strength of the biceps brachii in two samples (healthy individuals and poststroke patients with chronic hypertonic hemiparesis). It is hypothesized that manual acupuncture does provide neuromuscular stimuli to promote immediate changes in MU recruitment in healthy subjects or poststroke patients.

1 Methods and design

1.1 Study supervision This study protocol comprises a single-blinded randomized clinical trial with four parallel groups. This study protocol follows the recommendations of both the Consolidated Standards of Reporting Trials\textsuperscript{[10]} and Standards for Reporting Interventions in Clinical Trials of Acupuncture\textsuperscript{[11]}. Also, this study protocol follows the Declaration of Helsinki and is currently approved by the Augusto Motta University Center Institutional Committee of Ethics in research for execution (CAAE-0006.0.307.000-10). The flowchart of this study design is depicted in Figure 1.

![Flowchart of this clinical trial](image-url)
1.2 Participant eligibility with inclusion and exclusion criteria Inclusion criteria for healthy volunteers (health group, HG) are age equal to or greater than 20 years (both sexes), and the absence of pain, acute inflammation or trauma in the upper limbs, pregnancy, aversion to needles, undiagnosed or apparent medical conditions (for example, peripheral circulatory disease, coagulation disorders, malnutrition, systemic hypertension). Inclusion criteria for poststroke patients (case group, CG) comprise all those valid to HG plus diagnosis of ischemic or hemorrhagic stroke confirmed by image examinations, chronic (>6 months) upper limb partial motor impairment, ability to pose the affected elbow in range 80° to 100°, and absence of mental disorders that compromise understanding, communication and implementation of the experimental protocol. Exclusion criteria comprise incomplete responses on the assessment questionnaire, incomplete acquisition of the pre- or post-intervention sEMG signal (characterized by the absence of two-out-of-three periods of muscle activation) and low signal-to-noise ratio (characterized as the absence of visual detection of sEMG periods of muscle contraction).

Healthy volunteers will be selected among the academic graduating community and data will be collected at the Laboratory of Human Movement Analysis at the Augusto Motta University Center. Poststroke patients will be referred from Fluminense Association of Rehabilitation (AFR) and data will be collected at the rehabilitation gymnasium. All subjects will read and sign the written consent form after explanation on the research aims and methods.

1.3 Procedures and interventions

1.3.1 Phase one: sample screening All volunteers will be asked to answer questions regarding their clinical status in a questionnaire form that describes TCM patterns related to stroke patients. Items in the questionnaire for pattern differentiation are considered as dichotomous variables that will be used as input variables for the regression equations provided by the authors. Also, pattern differentiation will be performed by the pattern differentiation algorithm validated to zang-fu patterns. All volunteers will be characterized by age, sex, and the following clinic and anthropometric variables. Weight and height will be measured by analog scale and stadiometer, respectively. Heart rate will be measured by pulse palpation and digital chronometer. Systolic and diastolic blood pressure will be measured by aneroid sphygmomanometer. CG will be additionally characterized by stroke etiology (annotated from the patient’s medical prontuary), lucidity, orientation, and communicability (observed during clinical examination).

1.3.2 Phase two: acupuncture intervention and electromyographic evaluation Volunteers will sit on a chair with support for the upper limb to pose the elbow at 90° (flexion) throughout this study. Acupuncture and signal acquisition will be conducted by a physical therapist, specialized in acupuncture and with 16 years of clinical practice. The experimental protocol will consist of five steps. (1) Locating acupoints according to modern standards and skin locations will be cleaned with sterile cotton soaked with alcohol (70%) and moistened in saline solution (0.9%) for safety of the patient and improvement of sEMG signal conductivity. (2) Positioning of adhesive electrodes (double-disk, Ag/AgCl, diameter = 10 mm; inter-electrode distance = 20 mm; Hal Industria, SP, Brazil) for sEMG signal acquisition at the biceps brachii (short head). sEMG signals will be collected by an analog device EMG400C (EMG System, SP, Brazil) connected to a data acquisition card NI-6009 (14 bits, National Instruments, Texas, USA) and a computer. All electrodes will be fixed with adhesive tape to minimize artifacts produced by movements of the skin. Maximum isometric force will be measured by a load cell (0 to 200 kg; EMG System, SP, Brazil) connected to the same amplifier, fixed on the ground at 90°. (3) Synchronous acquisition of sEMG and isometric force signals at a sampling rate of 1.0 kHz per channel. To record and process the signals, algorithms written in LabVIEW (National Instruments) Windows will be used. Volunteers will execute 3 repetitions of a MIVC of the biceps brachii muscle during 5 s, followed by 2 min to allow resting and metabolic recovery. (4) Unilateral, slanted puncture (45°) of acupoint towards the direction of qi circulation with a sterile, disposable stainless steel needle (Lizhou, China; 0.20 mm × 13 mm) at approximately 1.5 cm depth. Following insertion, the needle will be rotated clockwise until volunteers report the Deqi sensation. Manual stimulation consisting of rotating the needle clockwise for 10 s will be performed after needle insertion, 5, 10, 15, and 20 min, and should be accompanied by the report of Deqi sensation. (5) The needle will be removed 20 min after insertion and then step 3 will be repeated.

1.4 Rationale for acupoint selection Two acupoints will be selected for this research on the basis of previous studies on acupoint prescription for stroke-related disorders. The acupoint, Quchi (LI11), is among the most cited acupoints among premodern authors and modern research. Also, LI11 presents traditional functions and location related to motor impairments in poststroke patterns. Tianquan (PC2) will be selected as a control acupoint mainly because of its location.

1.5 Outcome measures

1.5.1 Primary outcome measures The primary outcome measure of this study is the RMS value estimated from sEMG signals and MIVC values. All signals will be stored for off-line processing by another author. sEMG signals will be bandpass filtered (cut-off frequencies: 5 to 450 Hz, Butter-
worth 2nd order, in direct and reverse order) and an automatic, double-threshold method \((25)\) will be used to detect periods of myoelectric activity before estimation of RMS on each detected epoch. The average value of all detected epochs will be used as a representative value of RMS. Force signals will be lowpass filtered (cut-off frequency: 5 Hz, Butterworth 2nd order, in direct and reverse order) and synchronously segmented with sEMG. The maximum value among all detected epochs will be used as a representative value of MVC. No normalization will be performed on the sEMG signal amplitude.

1.5.2 Secondary outcome measures Secondary outcome measures of this study comprise the frequency of patterns in each group, as well as the frequency distribution of manifestations. Additionally, by comparison of the estimated probabilities of the linear regression model \((26)\) between HG and CG, a cut-off value will be determined and its accuracy evaluated in the studied sample.

1.6 Sample size Sample size estimation was based on equations for binary outcomes between two proportions (RMS decrease or not), considering \(a = 5\% \quad (Z_a = 1.96; \text{significance level})\) and \(\beta = 80\% \quad (Z_\beta = 0.84; \text{power of test})\) \((27)\). A sample size of 36 subjects is necessary to observe reduced RMS values on at least 80% of the sample after acupuncture at LI11 (intervention acupoint) as compared to a 50% (random) probability in the group after stimulation at PC2 (control acupoint). The calculated sample size is inflated by 10% to account for potential losses, yielding 39 healthy and poststroke individuals.

1.7 Randomization and blinding Four parallel groups will be randomly generated using a web-based random number generator. Two sets of numbers (one per group) with 39 numbers each will be sorted, annotated and inserted into envelopes that will be sealed before distribution to volunteers by the author. Envelopes contain one of the following guidance for intervention: PC2 in the nondominant arm of healthy individual, LI11 in the nondominant arm of healthy individuals, PC2 in the paretic upper limb, and LI11 in the paretic upper limb. Volunteers will receive their envelope in order of arrival. The researcher will open the envelope to determine the guidance for acupuncture but will not report to the patient the actual acupoint name. Signals will be stored without referring to the selected acupoint to allow a blinded signal processing of sEMG data by another author.

2 Discussion

This work proposes a study design protocol for evaluation of the immediate effects of acupoints manual stimulation on the biceps brachii electrical activity and isometric strength in healthy individuals and poststroke patients. Several difficulties arise when planning a study design with an integrative approach and these are discussed here.

Although pattern differentiation has been used to increase the efficacy of TCM intervention \((28)\), it was decided not to base acupuncture prescription on the identified pattern until a clear evidence of neurophysiologic effect is observed. Moreover, single acupoints and none complex prescriptions are proposed to avoid confusion bias on the expected physiologic effect. LI11 is among the top three acupoints most cited by both premodern and modern TCM researchers and therefore it is considered as a representative site for stimulation of muscles in the upper extremities. From another aspect, sEMG signals present limitations that may influence the interpretation of physiologic responses to acupuncture such as crosstalk, dependency on voluntary activation of muscles, and high inter-subject variability \((29)\). Additionally, normalization of sEMG is often a necessary step for reducing inter-subject variability but it will not be performed because both pre- and post-test conditions comprise MVC. It is considered that analyzing the dichotomous status (decrease or increase of RMS values) is an adequate substitute to account for the inherent inter-subject variability on sEMG values.

Planning clinical trials with an integrative design is challenging but is a necessary task to investigate TCM therapeutic effects. It is expected that new insights will be provided by this study design regarding the neuromuscular effects of manual acupuncture in both healthy and poststroke subjects.

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4 Competing interests

The authors declare that they have no competing interests.

5 Author’s contribution

Ana Paula de Sousa Fragoso designed the study, performed questionnaire interview, evaluated the subjects for enrollment in the study, and drafted the manuscript. Arthur de Sá Ferreira designed the study, developed the computational methods for pattern differentiation, performed the statistical analysis, and drafted the manuscript. Both authors revised and approved the final version of the manuscript.

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“徒手针刺影响健康人和中风后遗症患者肱二头肌功能的即时效果的平行随机对照试验”的研究方案

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背景：中风作为一种疾病，中医早在2000多年前就有诸多经典著作对其进行描述。然而，大部分有关针刺对中风后遗症患者功能恢复的疗效的临床对照试验均得出针刺具有长期疗效的结论，并非偶然。很多试验以表面肌电图测量患者骨骼肌的电活动以评定针刺刺激的即时疗效的研究结果也不一致。这些研究结果对针刺在神经营养水平的作用提出了质疑。本研究旨在比较徒手针刺影响健康人和中风后肌张力亢进患者的肱二头肌功能及力量的即时效果。

方法与设计：本研究计划开展含有4个平行对照组的随机单盲临床试验。分别针刺健康受试者及中风后遗症患者肱二头肌的等长张力作为主要结局指标。次要结局指标包括每组中医证候的出现频率及频率分布。

讨论：本研究的临床试验设计在方法学上较之前的类似试验有所改善。预计这一研究能够证实针刺刺激对健康人及中风后遗症患者的神经营养的作用。

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