

Effects of Radial Extracorporeal Shock Wave Therapy on Flexor Spasticity of the Upper Limb in Post-stroke Patients: Study Protocol for A Randomized Controlled Trial

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Study protocol

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Abstract

Background: Flexor Spasticity of the Upper Limb is common in post-stroke patients and seriously affects the recovery of upper limb function. However, there are no standard management protocols for this condition. Radial extracorporeal shock wave therapy (rESWT) is widely used as a non-invasive treatment method for various diseases, but its efficacy in reducing spasticity remains undefined.

Methods/design: A prospective, randomized, double-blind controlled trial is to be performed to study the efficacy of rESWT on the treatment of upper limb spasticity after strokes. One hundred participants will be recruited from the Inpatient department of Zhujiang hospital for this study. Patients who meet the inclusion criteria will be randomly allocated to either receive 3 sessions of active rESWT (Group A) or sham-placebo rESWT (Group B) with three day intervals between each session. Assessment will be performed at baseline and at each of the post-rESWT time points (t1, t2 and t3). The primary assessment outcome will be the Modified Ashworth Scale, while the secondary assessment outcomes will include surface electromyography, MyotonPRO digital muscle function evaluation and infrared thermal imaging.

Discussion: This trial is aimed at analyzing the application of rESWT for the management of spasticity after stroke via comprehensive and quantitative assessments. We hypothesized that after receiving active rESWT, patients will show greater improvement of upper limb muscles, compared with patients of the sham-placeborESWT group. The rESWT would be an attractive alternative to traditional methods and the results of this study may provide guidance and support for the further study of potential mechanisms.

Background

Flexor Spasticity is common in post-stroke patients with upper limb dysfunction, and seriously affects the recovery of upper limb function [1], while placing a significant mental and financial burden on the patient, caregivers and society [2]. The mechanisms underlying this disorder may involve the loss of inhibition of the cerebral cortex and other higher areas of the central nervous system after lesion to the central nervous system[3], and changes in muscle properties [4, 5] (e.g. stiffness, fibrosis and atrophy). Aggressive and appropriate spasticity management contributes to motor re-learning and function recovery during chronic stages [2, 6]. Currently, mainstream interventions for upper limb hypertonicity, include stretching, oral antispasticity medications, focal botulinum toxin (BTX) injections and surgical treatment [6–9]. However, the above treatment methods have drawbacks or are controversial, in terms of their effectiveness and safety [7, 10–12].

An extracorporeal shock wave is defined as a sequence of single sonic pulses with high peak pressure [13, 14], which can cause energy gradient differences and torsional tension between tissues of different densities through energy conversion and transmission, and form a cavitation effect for work, which induces a biological effect [15]. During the past few decades, extracorporeal shock wave lithotripsy [16] has been widely used and has evolved to be standard therapy used for urinary calculi due to its excellent efficacy, non-invasiveness and lack of obvious complications. At present, rESWT has also been widely

used for the treatment of various neurological and musculoskeletal diseases [17, 18], such as cerebral palsy [19], multiple sclerosis [20], tendinopathy [21], chronic tennis elbow [22] and nonunion of long bone fracture[23]. Recently, several studies [24–26] have indicated that extracorporeal shock wave could be used for decreasing hypertonia in strokes. However, only a few convincing studies [27] have been published as yet, and its exact mechanism remains unclear. Therefore, a prospective large-sample randomized double-blind controlled trial is needed to further confirm its efficacy. We hypothesized that the application of radial extracorporeal shock wave therapy will have a positive effect on the management of limb spasticity after stroke.

The Modified Ashworth Scale (MAS) [28, 29] is the most widely used clinical scale to grade spasticity and shows high inter- and intra-rater reliability for the assessment of muscle tone of upper extremities. Electromyography (EMG) H reflex can objectively evaluate changes in the excitability of α -motor neurons before and after treatment. Motor nerve conduction velocity (MCV) is a diagnostic technique used to assess peripheral nerve conduction function. By detecting the MCV of the median nerve before and after rESWT stimulation, we can observe whether the peripheral nerve has been damaged and determine the safety of the ESWT procedure. Surface electromyography (sEMG) can reflect the overall situation of muscle activity by placing surface electrodes on the muscle to collect electrical signals [30]. The sEMG indexes of root mean square (RMS), integrated electromyogram (iEMG) and co-contraction ratio (CR) [31] can be used to assess muscle spasm objectively and quantitatively. The MyotonPRO digital muscle function assessment system is a new non-invasive instrument that can be used to evaluate the functional status of skeletal muscles and biological soft tissue. It can quantitatively measure muscle tension, elasticity and other functional conditions [32, 33]. A previous study [34] has shown that ESWT can improve trophic conditions of spastic muscles. The infrared thermal imaging (IRT) system detects local nutrient status changes in spasmodic muscles of the upper limbs, which are associated with blood microcirculation and surface temperature distribution [35, 36]. Therefore, this trial is designed to use the above mentioned assessment techniques to examine the efficacy and safety of rESWT for the treatment of upper limb spasticity after stroke.

Methods/design

Trial design

This study is a prospective, double-blind and randomized controlled trial (RCT) that conformed to Standard Protocol Items of the Recommendations for Interventional Trials (SPIRIT) guidelines [37] (Additional file 1). The work flow chart of the procedure to be followed in this study is shown in Fig. 1. The participants are observed during their hospital stay and are randomly assigned to either receive 3 rounds of treatment with active rESWT (Group A) or sham-placebo rESWT (Group B). Assessments are to be performed at baseline and at each post-rESWT time point (t1, t2 and t3).

Study setting

The study setting is the Department of Rehabilitation Medicine at the Zhujiang Hospital of Southern Medical University, Guangzhou, China.

Inclusion criteria

Participants will be qualified for inclusion when they meet the following criteria: (1) meeting the "criteria for the diagnosis of cerebrovascular diseases" adopted by the Fourth Academic Conference on Cerebrovascular Diseases in 1995 [38], and confirmed using CT or MRI examination of the head; (2) an age between 35 and 75 years old, with a first episode and being in a stable clinical condition; (3) the presence of hemiplegic upper limb spasticity, at minimum grade 2, determined by MAS [28]; (4) no obvious cognitive impairment; (5) the informed consent form (ICF) being completed by the patient.

Exclusion criteria

(1) having received prior treatment for decreasing spasticity, including oral antispasmodic drugs, BTX injections and surgical treatment; (2) uncontrolled hypertension; (3) patients with chronic heart failure, malignant arrhythmia and other severe organic heart diseases; (4) patients with a pacemaker and other electronic implants; (5) the presence of coagulation dysfunction; (6) patients with local infections and skin rupture; (7) refusal to participate in this study.

Interventions

Active rESWT intervention (Group A): Patients are to be treated in the supine position on the area of the biceps, the radial flexor digitorum and the pronated round muscle after their affected side has been marked and the skin has been prepared using an alcohol soaked cotton. The couplant is to be evenly applied onto the treatment probe and a medium to high intensity pressure is to be applied to keep the probe close to the muscle belly. The following protocol is to be used: 2000 shots with a pressure of 0.2 MPa and a frequency of 8 Hz on each marked position, for a total of 3 rounds of treatment, once in 3 days.

Sham rESWT intervention (Group B): The protocol to be used is the same as that of "Group A", except that pressure to be applied is to be 0.1 MPa and no couplant is to be used on the treatment site, while a thick layer of gauze is to be placed between the skin and the probe instead, with no pressure applied.

The physiotherapist who is to perform the intervention should have received standardized training and must be familiar with the process and details of the intervention. The patients are all required to undergo the same routine therapeutic program (including common physical therapy and occupational therapy).

Outcomes

Primary outcome assessment: MAS. The scale is graded in 6 stages, ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension). For convenience of statistical analysis, a MAS grade of 1+ is to be substituted with a value of 2, while grades 2, 3, and 4 are to be substituted with values of 3, 4 and 5, respectively.

- (1) Recovery: Muscle tension had completely returned to normal;
- (2) Obvious effect: The muscle tension had not returned to normal, but muscle tension had decreased by 2 levels;
- (3) Effective: Muscle tension had decreased by 1 level;
- (4) Inefficacy: No change in muscle tone pre and post treatment.

Secondary outcome assessments:

Electromyography (EMG), surface electromyography (sEMG), MyotonPRO digital muscle function evaluation system and infrared thermal imaging (IRT) are to be used for the evaluation.

1. EMG evoked potentiometer

(1) H reflex. H reflex of the median nerve is to be detected using a EMG evoked potentiometer. The recording must be conducted from the flexor carpi radialis as follows: the recording electrode is to be placed at the mid-upper 1/3 junction of the medial humeral epicondyle and the radial styloid process line, the reference electrode is to be placed at the tendon, the earth electrode is to be placed at the olecranon, and the stimulation electrode is to be placed near the brachial artery of the elbow. The maximal amplitude of H-reflex (H-max) and M-response (M-max) are to be recorded. The H-max/M-max value, which can reflect the excitability change of the alpha motor neuron, is to be calculated, in order to detect changes in the response to the effect of rESWT on the spasmodic muscle.

(2) Motor nerve conduction velocity (MCV). The same apparatus is to be used, but the electrodes are to be placed differently. The recording electrodes must be placed on the thumb short abductor muscle belly and the stimulating electrode must be placed on the wrist and elbow median nerve to record distal motor latency (DML), MCV and amplitude of brachio- abductor pollicis brevis. This assessment is aimed at determining whether rESWT causes nerve injury and to assess its safety.

2. Surface electromyography (sEMG)

(1) Root-mean-square value (RMS). A sEMG recording is to be obtained using bipolar Ag/AgCl surface electrodes (MyoMove, Northam Electric Co., Ltd., Shanghai, China) for the sEMG assessment. The patient is to be treated while in a sitting position with their upper limbs comfortably placed on the treatment table. The electrodes are to be placed on the fullest part of biceps brachii and flexor carpi radialis muscle belly. The locations at which the stimulating and recording electrodes are to be placed must be rubbed with 70% alcohol to reduce skin impedance. Electrode placement is to be done as recommended by SENIAM (Surface EMG Noninvasive Muscle Assessment) and ISEK (International Society of Electrophysiology and Kinesiology). The resting sEMG activity of the biceps brachii and flexor carpi radialis are to be measured under stable and static conditions for 30 seconds at a time. The RMS of biceps brachii and flexor carpi radialis must also be measured. RMS can be used to objectively and

quantitatively evaluate the condition of muscle spasm, with a higher value indicating more severe muscle spasm.

(2) Integrated electromyogram (iEMG) and co-contraction ratio (CR)

For the sEMG assessment, a sEMG recording with bipolar Ag/AgCl surface electrodes is to be used (Northam Electric Co., Ltd., Shanghai, China). The patients are to be treated while sitting on a chair with their elbow at a 45° flexed position and wrist in a neutral position. The electrodes are to be placed on the fullest part of the biceps brachii muscle (BM) and triceps brachii muscle (TM) belly. Before the electrodes are attached, the skin is to be prepared using 70% alcohol to reduce skin impedance. Electrode placement must be done as recommended by SENIAM and ISEK. Training is to be performed for 1 minute before the assessment to help patients familiarize themselves with the process. During the test, the patient are to be asked to stretch the elbow joint with maximum strength for 10 s, in order to measure maximum isometric voluntary contraction (MIVC) [39]. The iEMG and CR of BM and TM are to be recorded for 20 s and 5 s before and after contraction, respectively, as the basic control. The test is to be carried out 3 times, with an interval of 5 minutes between each application, and the maximum value is to be recorded. The assessment includes the iEMG of the BM and TM when the elbow is stretched for maximum isometric contraction, and then the CR is calculated. The iEMG value can reflect the total amount of muscle discharge per unit time, and is mainly used to analyze the contraction characteristics of muscles per unit time. CR refers to the proportion of antagonist muscles during the process of active muscle contraction [31], while it is well known that increased synergistic contraction of antagonistic muscles is a common phenomenon in stroke patients. The decrease of CR within MIVC of the elbow indicates a reduction in the strength of the biceps tendon.

$$\bullet \text{ CR} = \frac{\text{iEMG of BM}}{\text{iEMG of BM} + \text{iEMG of TM}} \times 100\%$$

3. MyotonPRO Digital Muscle Function Assessment System (Muomeetria Ltd., Tallinn, Estonia, EU)

This evaluation system performs a non-invasive measurement of the functional state of skeletal muscles and biological soft tissues, which can quantitatively assess the functional status of muscle tension and elasticity [40, 41]. The patient is asked to completely relax while lying in the supine position on a mat, with the forearm in the mid position and the elbow joint extended (if the muscles cannot be fully extended, the forearm is supported on both sides to maintain the forearm neutral position). The measurement point of the biceps humerus is tested perpendicular to the skin surface. Measurement is taken once every 1 minute, for 3 times in total, and the average is obtained. The parameters required are [42]: F - natural damped oscillation frequency [Hz] to describe muscle tension; C - Deborah number, the ratio of muscle relaxation time to deformation time; R - Muscle internal mechanical pressure release time [ms]; as well as C and R reaction to the viscoelasticity of the muscle.

4. Infrared Thermal Imaging (IRT)

A non-invasive and non-contact infrared thermal imaging system (Baotonghua Medical Devices Co., Ltd. Chongqing, China) is to be used to detect changes in local nutritional status related with blood microcirculation and surface temperature distribution. The instrument has a thermal sensitivity of 0.1°C. Prior to measurement, all clothes covering the area to be examined must be removed and the patients are allowed to adapt to the room over a period of 15–20 minutes. The room is to be kept quiet with a temperature ranging from 22–27°C and relative humidity below 45%. Then, a thermovision camera is positioned perpendicular to the area of the biceps surface on the anterior side of the upper arm. The IRT value is obtained in degrees Celsius [°C]. The lower the surface temperature, the worse local blood circulation and nutritional status.

Participant timeline

The schedule of enrollment, intervention and assessments are shown in Figure. 2.

Participants

Patients with Flexor Spasticity of the Upper Limb after stroke.

Recruitment

Direct recruitment from Zhujiang hospital.

Sample size

The known effectiveness of post-stroke spasticity treatment using conventional methods is 64.5%, while preliminary experiments with ESWT have shown an expected effectiveness of 80%, with two-tailed tests of a significance level of $\alpha = 0.05$ and $\beta = 0.1$, which is expected to fall off at a rate of 10%, using professional software Advisor nQuery sample size estimation, for a sample size of 45 cases in each group, which can be considered as a loss rate of about 10%. Therefore, for this study, a sample size of 50 cases in each group was decided on, with a total sample size of 100 cases.

Randomization

Eligible patients are to be numbered sequentially based on enrollment sequence and are to be randomly assigned to Group A (active rESWT) or Group B (sham-placebo rESWT), with a total of 50 patients in each. Random numbers are to be generated using a computer software program run by an external statistician. Each of the random numbers along with the group assignment are to be written on a piece of paper and enclosed in a sealed envelope.

Blinding

This study uses a double-blinded design, in which interventions are performed by one physiotherapist and patients are evaluated by another physician, who is unaware of the treatment or grouping. Neither of them will participate in the subsequent data analysis.

After the statistical judgment is completed, unblinding will be performed to expose the experimental group and the control group. In general, emergency unblinding is not considered.

Data collection methods

The evaluation index is to be collected before and after treatment is performed on all patients, with raw data recorded on case report forms (CRFs) in a timely, complete, accurate and clear manner. In order to improve subject compliance, subjects who can complete the entire procedure in accordance with the protocol are to be provided with additional rehabilitation assessments and rehabilitation

recommendations. If a participant chooses to withdraw, they will be asked to provide reasons and the reasons for withdrawal are to be recorded.

Data management

An EPIDATA 3.2 database will be used to manage data, for which input and proofreading will be performed by two researchers independently, leading to double data entry and storage.

Statistical methods:

The primary comparisons for MAS will be made using repeated measures mixed effect model with terms of treatment, time and corresponding baseline values as covariates. We will first examine the intervention by time interaction, and then proceed to a main effects model with only group and time.

The independent t-test will be used to compare changes between active rESWT intervention and sham rESWT intervention groups from baseline to the end of follow-up when data are normally distributed, and the Mann-Whitney u test will be used when data are not normally distributed. A Chi-square test will be used for dichotomous variables.

In secondary analyses, repeated measures mixed model will also be used to examine the associations between treatments and repeated outcome measures. Additionally, linear regression and/or logistic regression analyses will be employed to assess the associations between treatments and changes or increases in outcomes from baseline to the end of follow-up in univariate and multivariate modelling adjusted for relevant covariates.

All data will be analyzed using intention-to-treat principles. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and nonresponses. Per protocol analyses will also be performed in the participants who complete other assessments include Hmax/Mmax, MCV, RMS, iEMG, CR, MyotonPRO and IRT. Statistical analysis will be performed using SPSS software (version 20.0) and the significant level set at $p < 0.05$.

Data and safety monitoring

Original CRFs will be archived and stored with corresponding subject codes after the completion of data entry and review. A Data Monitoring Committee (DMC), composed of clinicians and biostatisticians, without any competing interests, will monitor the safety and progress of the trial.

Harm and Audit

The researchers are obliged to take necessary measures to protect the safety of the subjects. If an adverse event (AE) occurs during the trial, the investigator should take appropriate measures, record it in the CRF, and explain whether it has a correlation with the intervention. The incidence of AEs between Group A and B should be compared after the trial. If serious adverse events (SAEs) occur during the clinical trials, the investigator should immediately take appropriate treatment measures and report to the sponsor, the Ethics Committee (EC) and DMC in a timely manner.

During the trial, Tao Fan will be responsible for communicating with relevant parties (such as other investigators, trial participants, journals and regulatory authorities), if there is a need for subsequent modification of important experimental protocols, and any modification of the trial protocol should be approved by the EC. The EC and DMC will periodically review the experimental behavior to safeguard the rights of the subjects involved in the clinical trial, to ensure the accuracy and completeness of the test records and reported data, and to ensure consistency with the protocol approved. If SAEs caused by

interventions occur during the trial, the EC has the right to propose a modification of the trial protocol or even terminate the trial.

Trial status

This is the second version of the study protocol dated on October 20, 2017. This trial was registered on May 14, 2018. The first patient was recruited on October 18, 2018. At the time of manuscript submission, a total of 10 patients have been recruited, and we hope to complete recruitment within 3 years. After patient recruitment is completed, all data will be statistically analyzed, and a research article will be written and submitted.

Discussion

Stroke survivors with spasticity suffer substantial mental, physical and financial stress. Effective spasticity treatment will likely increase their functioning and their health-related quality of life. Clinical studies [43–45] have shown that ESWT may improve the muscle spasm of stroke patients without serious adverse reactions. Many studies conducted in recent years have been investigating the biological effects of ESWT. In the past, the mechanism by which ESWT acts on musculoskeletal diseases was assumed to be mechanical decomposition, just like extracorporeal shock wave lithotripsy. However, further clinical observations and experimental results, have suggested that ESWT can promote neovascularization, the release of growth factors, the differentiation of mesenchymal stem cells and the production of endogenous nitric oxides (NOs) [46–48], which can decrease the intrinsic stiffness of connective tissue, increase muscle elongation, improve tissue microcirculation and change the formation of neuromuscular junctions of the peripheral nervous system [49–51], in order to achieve encouraging clinical results.

Based on the propagation pattern of the waves, extracorporeal shock wave therapy can be classified as focused extracorporeal shock wave therapy (fESWT) and rESWT. Compared with fESWT, which can penetrate and focus its energies much deeper into the tissue, rESWT has a more superficial effect. Wu et al. [52] compared the effect of fESWT and rESWT for the treatment of spastic equinus in patients with stroke and concluded that the effect of rESWT is superior to that of fESWT, in terms of improving the ankle passive range of motion and plantar contact area during gait, while both showed similar improvement of the spasticity of the gastrocnemius muscle. Other significant differences in their clinical application effects are still being observed. The potential mechanism by which rESWT alleviates hypertonia remains undefined.

Through the use of new assessment techniques, this trial is designed to generate a considerable amount of outcome data and provide strong supporting evidence for the effectiveness of rESWT for the management of spasticity after stroke. We hypothesize that after active rESWT, patients will show greater improvement in upper limb muscles, compared with patients who have received sham-placebo rESWT treatment. rESWT would be an attractive alternative to traditional methods and the results could provide guidance and support for the further study of potential mechanisms.

Abbreviations

AE:adverse event; BM:biceps brachii muscle; BTX:botulinum toxin; CI:confidence interval; CR:co-contraction ratio; CRFs:Case report forms; DMC:Data Monitoring Committee; DML:distal motor latency; EC:Ethics Committee; EMG:Electromyography; ESWT:Extracorporeal shock wave therapy; fESWT:focused extracorporeal shock wave therapy; H-max:the maximal amplitude of H-reflex; ICF:informed consent form; iEMG:Integrated electromyogram; IRT:infrared thermal imaging; ISEK:International Society of Electrophysiology and Kinesiology; MAS:Modified Ashworth Scale; MCV:motor nerve conduction velocity; MIVC:maximum isometric voluntary contraction; M-max:the maximal amplitude of M-response; NOs:nitric oxides; rESWT:radial extracorporeal shock wave therapy; RMS:root mean square; SAEs:serious adverse events; SD:standard deviation; sEMG:surface electromyography; SENIAM:Surface EMG Noninvasive Muscle Assessment; TM:triceps brachii muscle.

Additional File

Additional file 1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: recommended items to be addressed in a clinical trial protocol and related documents*.

Declarations

Ethics approval and consent to participate

In order to ensure that this clinical study complies with the Helsinki Declaration and relevant Chinese regulations on clinical research, the Institutional Ethics Committee of the Zhujiang Hospital of Southern Medical University has approved our study (reference number: 2017-KFYXK-003). Subjects can only be included in clinical studies after they voluntarily sign the ICF. The researcher is committed to maintain the privacy of the patients.

Consent for publication

Each participant will provide informed consent for individual patient data to be published.

Availability of data and materials

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Competing interests

There is no funding/assistance from commercial organizations for this study. Tao Fan is the founder of this program. The other authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the design of the study protocol. TF is responsible for this study. GZH conceived and developed the study design. XYZ drafted the trial protocol and prepared the manuscript. PCH, PZ and MYW revised the protocol. XJZ, RDL, RHL and XZ are responsible for data acquisition and analyses. All authors have read and approved the final manuscript.

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Figures

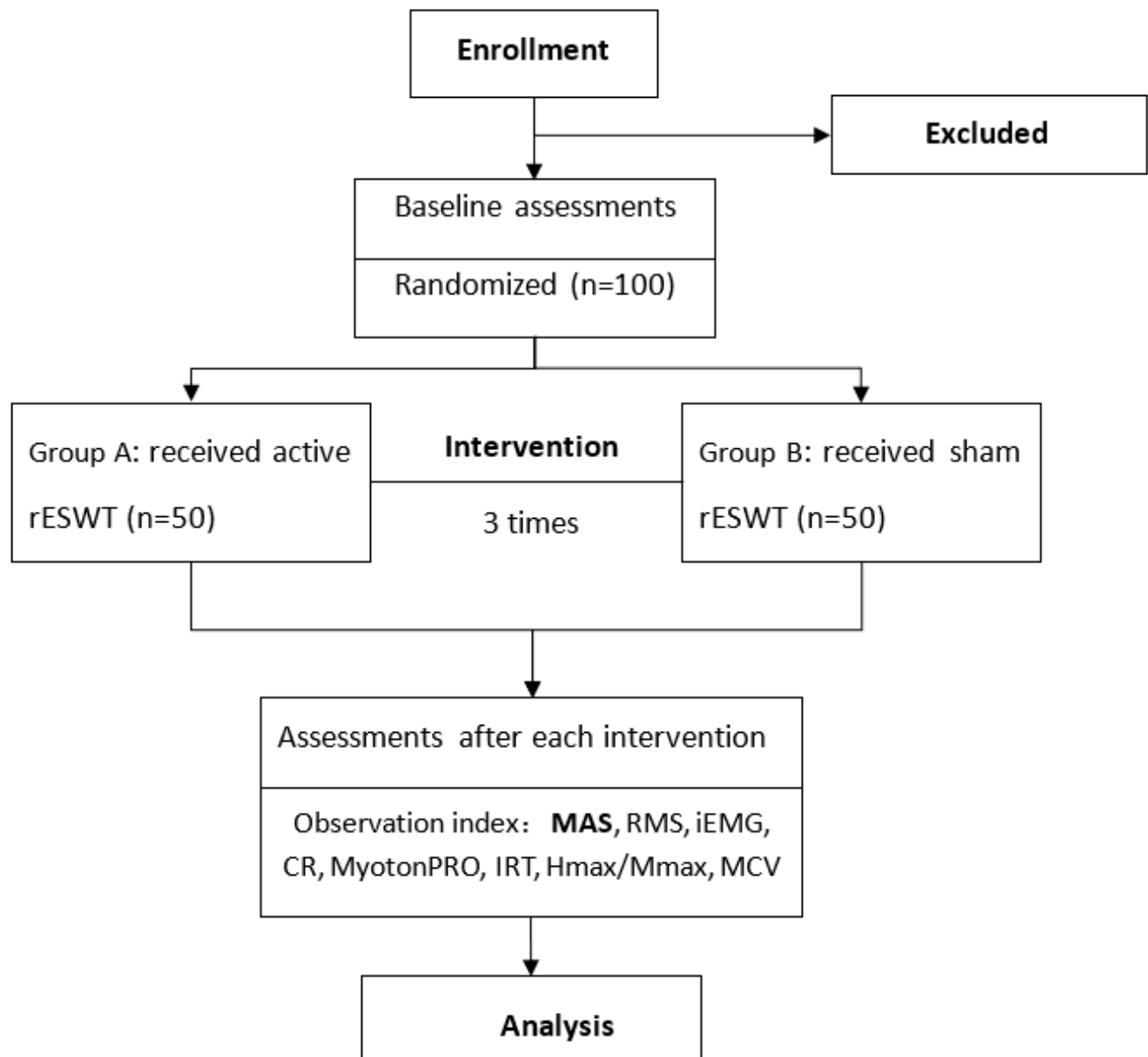


Figure 1

Work flow chart of trial participation

TIMEPOINT	STUDY PERIOD				
	Enrollment	Allocation	Post-allocation		
	-t1	Baseline	t1	t2	t3
Basic medical history	X				
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Group A			X	X	X
Group B			X	X	X
ASSESSMENTS:					
MAS		X	X	X	X
EMG(H reflex, MCV)		X			X
sEMG (RMS, iEMG, CR)		X	X	X	X
<i>MyotonPRO Digital Muscle Function Assessment System (F, C, R)</i>		X	X	X	X
IRT		X	X	X	X

Group A: active radial extracorporeal shock wave therapy.

Group B: sham-placebo radial extracorporeal shock wave therapy.

t1/ t2/ t3: after the first/ second/ third radial extracorporeal shock wave therapy.

Figure 2

The schedule of enrollment, interventions and assessments

Supplementary Files

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- [1SPIRITFillablechecklist15Aug2013.docx](#)