Effectiveness and brain mechanism of rTMS combined with quadriceps strength training in individuals with knee osteoarthritis: Study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Quadriceps training is necessary in function, activity of daily living and quality of life for patients with knee osteoarthritis (KOA) but it did not reduce the rate of surgical treatment (replacement of knee) for end-stage KOA in the long term. This may be related to brain structure changes and maladaptive plasticity in KOA patients. Transcranial magnetic stimulation (TMS), as a non-invasive brain stimulation technique, which uses magnetic pulse on the central nervous system, stimulates the excitability of nerve cells, enhances the functional connectivity of brain regions and improves maladaptive plasticity. However the therapeutic effect of two rehabilitation techniques combination in patients with KOA remains unclear. Therefore, the purpose of this study is to investigate whether the high-frequency rTMS combined with quadriceps strength training can improve the function in KOA more effectively than quadriceps training alone and explore the brain mechanism of this combined rehabilitation.

Methods: This study is an assessor-blind, sham-controlled, randomized controlled trial involving 12 weeks intervention and 6 months follow-up. One hundred and twelve participants with KOA will be received usual care management and randomized into four subgroups including quadriceps strength training (QT); high-frequency rTMS training (HT); sham rTMS and quadriceps strength training (ST+Q); high-frequency rTMS and quadriceps strength training (HT+Q). The rehabilitation interventions in four groups will be carried out 5 days per week for a total of 12 weeks. All outcomes will be measured at baseline, 4 weeks, 8 weeks, and 12 weeks during intervention and 1 months, 3 months and 6 months during follow-up period. The primary outcomes are visual analog scale (VAS) and isokinetic muscle strength test. Secondary outcomes are include Knee Injury and Osteoarthritis Outcome Score (KOOS) 36-Item Short-Form Health Survey (SF-36), rTMS and magnetic resonance imaging (MRI).

Discussion: The study will provide evidence for the effects and brain mechanism of high frequency rTMS on improving function in KOA patients. High frequency rTMS can be added into the muscle training program for KOA patients as a supplementary therapy content if it is proved to be effective.

Trial registration: Chinese Clinical Trial Registry ChiCTR2300067617. Registered on Jan.13,2023.

Background

Knee osteoarthritis (KOA) is a chronic degenerative joint disease characterized by degenerative cartilage lesions and secondary bone hyperplasia of the knee joint [1]. KOA accounts for more than 80% of the total osteoarthritis and leading cause of disability, decrease quality of life in the adult and elderly population[2]. Treatment for KOA is always lifelong, which causes a huge economic burden on individuals, families, and society. Therefore, exploring an effective treatment for patients with KOA is necessary for both individual and society.

To date, there is no any proven treatment method that can reverse the course of KOA[3]. Current therapeutic strategies for KOA are focus on improving muscle strength or relieving pain including

medication, physical exercise, intra-articular injection, etc. Clinical guidelines recommend physical exercise as the one of the most important non-pharmacological treatments of KOA[4], which has been proved to improve knee function effectively[5]. Quadriceps strengthening is an important component of the exercise program because it has been found that patients with KOA always have significantly quadriceps weakness[6]. Although exercise is effective in KOA, a recent meta-analysis indicated its treatment benefits are moderate for pain (effect size-0.56,) and function (0.50, 0.38–0.63), performance (0.46, 0.35–0.57) at or nearest to 8 weeks. Besides, the exercise effects appeared to peak around 2 months and then gradually decreased and became no better than usual care after 9 months[7]. It means the effects of exercise will get a plateau and pain always persist. Leandro etc. also have proved the exercise treatment effectiveness and adherence seem to decrease over time[8].

In recent years, more and more evidence has proved that low activation of M1[9] and secondary to gamma loop[10] and motor-sensory circuit disorders[11] may be potential brain mechanisms for weakness of quadricep muscles in KOA. It can be seen that the enhancement of muscle strength for KOA is not only about the improvement and optimization of muscle strength training program, but also about the activation of brain areas. Therefore, the M1 may be a potential neurotherapeutic target for therapy in KOA[12]. Furthermore, another study showed that chronic pain in KOA can also further increased motor cortex inhibition. The chronic pain in KOA patients is not necessarily related to damage to the peripheral muscular system, but rather to neuroplastic changes in pain-related circuits that result in maladaptive neuroplasticity and lead to a perpetuation of pain[13]. The neuroplasticity changes in response to constant peripheral pain and less intracortical inhibition, which lead to enhance the levels of pain and dysfunction[14, 15].

Therefore, the randomized controlled trial is designed to observe whether high frequency rTMS combined with quadriceps strength training can better improve the knee function and reduce pain in KOA patients than quadriceps strength training alone and explore the brain mechanism of this combined rehabilitation. The study will provide a new perspective on the treatment of KOA.

Methods

Study design

This study will be a randomized controlled trial with a parallel-group design. A total of 112 eligible participants will be assigned to the quadriceps strength training (QT group); high frequency rTMS (HT group); sham rTMS and quadriceps strength training (ST+Q group); high frequency rTMS and quadriceps strength training (HT+Q group) at 1:1:1:1 ratio using stratified randomisation with gender and age as factors. A brief flowchart of the entire study is shown in **Figure 1** and the schedule of events is provided in **Table 1**. The study protocol was approved by the Ethics Committee of Shanghai Seventh People's Hospital (2022-7th-HIRB-065) and registered in the Chinese Clinical Trial Registry (ChiCTR2300067617).

Table 1 Schedule of enrolment, intervention and assessments

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation			Follow-up		
TIMEPOINT**	*-1th week*	0	*4th week*	*8th week*	*12th week*	*1th month*	*3th month*	*6th month*
ENROLMENT:								
Eligibility screen	√							
Informed consent	√							
Demographic information								
Randomization· and Allocation		√						
INTERVENTIONS:								
ST Group			←	—	→			
HT Group			←	—	→			
ST +Q Group			←	—	→			
HT +Q Group			←	—	→			
ASSESSMENTS:								
VAS		√	√	√	√	√	√	√
TQPEAK TQPEAK/BW agon/antag		√	√	√	√	√	√	√
KOOS		√	√	√	√	√	√	√
SF-36		√	√	√	√	√	√	√
motor cortex excitability		√	√	√	√			
MRI scan		√			√			

Note: "√" means things will be done. **VAS**, Visual Analog Scale; **TQPEAK**, peak torque; **TQPEAK/BW**, TQPEAK adjusted for body weight; **agon/antag**, agonist-antagonist ratio; **KOOS**, Knee Injury and Osteoarthritis Outcome Score; **SF-36**, 36-Item Short Form Survey. **MRI**, Magnetic resonance imaging.

Sample size calculation

The sample size calculation was conducted using the G*power software (v3.1.9.2). According to a prior two-way analysis of variance (ANOVA) F-test, with a power of 0.80 and effect size of 0.25, an alpha (α) level of 0.05, an estimated 88 participants will be required. Considering a 20% drop-out rate, the final sample size of each group will be 28, with a total of 112.

Participants

Inclusion criteria

1. Meet the diagnostic criteria for KOA set by the ACR in 2019[16]
2. Age between 40 and 60 years old
3. Have a minimum score of 25 on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score
4. Sign an informed consent form

Exclusion criteria

1. Knee or hip arthroplasty
2. Any uncontrolled non-musculoskeletal conditions that would make testing difficult and uncomfortable such as unstable heart conditions
3. Neurological condition that affects lower-limb strength or walk (e.g., stroke)
4. Have a contraindication for TMS use such as: existence of metal in the skull or implanted devices, epilepsy history, pregnancy
5. Use of drugs that might affect cortical electrical activity (anticonvulsants, antidepressants or antipsychotics)
6. Have a contraindication for MRI use such as pacemaker, metal implant ect.

Drop-out criteria

1. Inability to return for treatment for any reason
2. Adverse events occur due to treatment
3. Participants who receive other intervention to treat KOA or other that may interfere with the results of this study

Recruitment, enrollment and randomization procedures

All patients with KOA will be recruited from the orthopedics or joint surgery department of Shanghai Seventh People's Hospital in China and communities around the hospital. Recruitment methods will include posters, online advertisements, and leaflets. We will communicate with prospective participants about the study details. After the patients voluntarily signs the informed consent, they will be invited to participate in the study. Recruitment will start from 1 October 2023, until when 112 participants are enrolled.

A total of 112 eligible participants will be assigned to four groups at 1:1:1:1 ratio using stratified randomisation with gender and age as factors in this research. The stratified randomisation will be achieved as follows: Firstly, participants will be invaded into men and woman two groups. Secondly, the two groups will be grouped by age including: men aged < 50; men aged≥ 50; women aged<50 and women aged≥50. In these four subgroups, the subjects will be randomly regrouped the QT group; HT group; ST+Q group and HT+Q group. Finally, all the four groups will be regrouped into new four groups to minimize the bias of the final results. The randomisation procedure is performed by an independent research assistant who is not involved in the data collection using Microsoft excel to generate the random number (https://www.microsoft.com).

Allocation concealment and blinding

Allocation concealment will be performed by using sealed, opaque envelopes which will hide a serial number. Additionally, an independent study researcher will open the envelopes in sequence after participates complete all baseline assessments to avoid selective bias. Due to the visibility of the quadriceps strength training intervention, physiotherapists and patients cannot be blind to intervention allocation. Therefore, the blinding will only be applied to the assessors and statisticians who responsible for data collection and final statistical analyses in this study to avoid implementation bias and measurement bias. Importantly, they will not participate in the participant recruitment process. The way to determine whether a blind method has been successfully implemented is by enquire the patient answer a question "Do you know which group you will be divided into before the follow-up evaluation is complete?" which is only using 'yes or no' to response. If the patient answer 'yes', we will ask he or she again "How did you know that?".

Interventions

All participants will receive usual care management, including health education and physical therapy when necessary. Six qualified physiotherapists who have attained the physical therapist's certification with over 5 years of experience will be trained beforehand, so as to instruct and guide patients in carrying out these exercises. The interventions in four groups will be carried out 5 days per week for a total of 12 weeks.

QT Group

In the QT group, the participants will receive 20 min quadriceps strength training intervention by using Biodex Multi-Joint System 3 dynamometer (Biodex Medicalt, Shirley, NY, USA). The 12 weeks intervention duration period has been chosen based on evidence that at least 12 sessions of supervised exercise are required for exercise to be effective in KOA, with a number of studies demonstrating symptom improvement in KOA after 8-12 weeks of exercise[17]. Thus, 12 weeks should be sufficient to show improvement in this population. We will modify the program according to the user's manual to reduce the risk of participants and check the device for calibration errors. All participants will be informed how the test would be and its purposes. They will conduct two familiarization sessions before the formal intervention to ensure that they feel comfortable during the exercises and perform the technique correctly. After familiarization sessions, participants will be instructed to sit in an isokinetic dynamometer and the V elcro® fixation straps will be tied around the chest, hip and the distal thigh of the training limb to prevent compensatory motion occurs. the dynamometer axis will be aligned with the canter of the lateral femoral condyle. The lever arm will be adjusted according to the training leg length and the resistance will be applied anterior to the ankle joint. The training knee will be kept at a 90° flexed position and they will be instructed to extended knee at angular velocity of 60°/sec, 90 °/sec and 120°/sec with 15 repetitions in 3 sets. Rest periods of 30 seconds between each test extension and 2 minutes between each velocity will be given. Training will perform 5 days per week for 12 weeks. A regular physiotherapist will conduct all isokinetic testing with verbal stimuli. Outcome parameters will be assessed by an independent evaluator, who is experienced in handling isokinetic devices[18]. The peak torque (TQPEAK), TQPEAK adjusted for body weight (TQPEAK/BW) and agonist-antagonist (agon/antag) ratio will be the outcomes.

HT Group

In the HT group, the participants will receive 20 min high-frequency rTMS training intervention. The rTMS will be performed with a Super-Rapid Magstim Stimulator (The Magstim Co., Whitland, UK) including a figure-8 type coil. the reason why we choose the figure-8 type coil is not only because it has stronger focus, but it reduce risk of seizures and other side effects than the h-coil and circular type coil[19]. And all of the rTMS program will be performed as the recommendations of the International Federation of Clinical Neurophysiology[20, 21]. The coil will be placed in the M1 area on the opposite side of the pain and uniformly in the left when the patient had bilateral knee pain as in previous rTMS studies[22, 23]. To determine the coil position, we first will place the center of the helmet to install the figure-8 type coil at a point 1 cm lateral and 1 cm posterior from Cz. Then, we will identify the location and angle of the helmet by identifying the minimum stimulator intensity needed to cause a motor response in the targeted lower limb. We will keep the front surface of the helmet facing forward to ensure that the coil orientation is the same. The resting motor threshold (rMT) will be defined as the lowest intensity that produced five responses with peak-to-peak amplitude of at least 50mv in ten consecutive trials. We will determine the coil position and estimation of MT before the high-frequency rTMS session and the parameters are as

follows: 10 Hz stimulation for 4s per session, with a 40s interval between sessions, 30 sessions per treatment, totaling 1200 pulses at 90% rMT over M1 of the target hemisphere.

ST+Q Group

In the ST+Q group, sham rTMS will be delivered with the coil angle rotated 90° and only one wing of the coil touching the scalp of the participant to avoid inducing real stimulation. The parameters, including noise, time, and frequency of the sham rTMS will be same as HT groups[24].Each patient will receive sham rTMS daily for five consecutive days.

HT+Q Group

In the HT+Q group, the participants will receive active High-frequency rTMS and quadriceps strength training intervention with randomization of treatment order. The parameters, including noise, time, and frequency of the High-frequency rTMS, will be the same as HT groups, and the detail of quadriceps strength training will be same as described above.

Outcomes

Participants will be assessed by other physiotherapists blinded to the group allocation at different time points based on different assessments shown in Table 1. Additionally, baseline age, gender, symptoms, disease severity, duration, previous treatment and medication will be recorded using a questionnaire (in week 0). Besides all side effects during the study also will be recorded in real time.

Primary outcomes

VAS

The Visual Analog Scale (VAS) will be used as one of the primary outcomes to evaluate the improvement of knee pain, which consists of a 10-cm line, where 0 represents “no pain” and 10 represents “worst possible pain”. The participants will be asked to recall knee pain related to knee joint movement in the previous week and mark on the line. The reliability and validity of the VAS in application of musculoskeletal conditions is proved good[25].

Muscle strength

The maximal isokinetic muscle strength will be assessed by the Biodex Multi-Joint System 3 dynamometer (Biodex Medicalt, Shirley, NY, USA). Isokinetic exercise is a mode of speed-constant training, which can be used at low, moderate and high velocity for different evaluations and rehabilitation

programs and provides reliable data. It is actually always used to quantify muscle strength, treatment and rehabilitation efficacy with mechanical or neurological instability of the knee or ligament injury[26].

Secondary outcomes

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The Knee Injury and Osteoarthritis Outcome Score (KOOS, http://www.koos.nu) is a questionnaire which is a self-administered and participants need approximately 10 minutes to answer all questions[27]. Different from Western Ontario and McMaster Universities Arthritis Index (WOMAC), KOOS has a more comprehensive assessment including five subscales pain, symptom (stiff) activity of daily living, physical function, quality of life. Every question has a minimum score of 0 and a maximum of 4 points. After the score of each part is calculated separately, it is converted into a percentage score by the conversion formula. 0 points of the converted percentage score means that the function of this part of the joint is very poor, while 100 points means that the function of this part of the joint is completely normal[28]. The KOOS shows good validity and reliability for patients with mild to moderate KOA[29].

36-Item Short-Form Health Survey (SF-36)

The SF-36 is the secondary outcome measure which is a health-related questionnaire developed by the Boston Institute of Health and used to assess the quality of life (QOL) with high reliability and validity[30]. The scale is divided into physical health QOL and mental health QOL and including 36 questions in total. The former consists of physical function, social function, physical role function and emotional role function, The latter contains mental health, energy fatigue, pain, and general health. The scale assess QOL over the past month and the score of the SF-36 is 0–100 with higher scores indicating better QOL. [31].

motor cortex excitability

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation tool is a commonly used to measure the functional level of cortex excitability and physiology in vivo[32-34]. The motor evoked potential (MEP) is an important index marker of corticospinal excitability which means when magnetic stimulation over M1, the descending pathway produces excitability and contralateral muscle contraction of the recorded value. The cortical silent period (CSP), which represents momentary suppression of MEP due to GABAergic. The short intracortical inhibition (SICI) and intracortical facilitation (ICF) which represent inhibitory and excitatory activation of interneurons within the motor cortex thought to probe GABAA-mediated inhibition and glutamatergic facilitation[35].

Magnetic resonance imaging (MRI)

MRI scan will use a 3.0-T GE scanner (General Electric, Milwaukee, WI, USA) with an eight-channel phased-array head coil at Medical Imaging Department of Shanghai Seventh People's Hospital in China.

Two independent MRI scans will be performed on each participant at baseline and after the 12-week intervention. Before the MRI evaluation, the scanner will require the participant to rest for 10 minutes and participants will be asked to stay awake with eyes closed during the entire MRI scan.

Resting state functional MRI images (Rs-fMRI) will be acquired with the following parameters: TR=2100 ms, TE=30 ms, flip angle=90°, voxel size=3.125 mm×3.125 mm×3.6 mm, 42 axial slices, field of view (FOV)=200mm×200 mm, phases=230. We also collected high-resolution T1-weighted structural images(T1WI), using a 3D-BRAVO sequence with the following parameters: TR=8.2 ms, TE=3.2 ms, flip angle=12°, FOV=220mm 20 mm, Matrix=256,256, slice thickness=1 mm[36]. The MRI outcomes include the following: grey matter (GM) density, white matter (WM), subcortical nuclei volumes, cortical thickness; functional connectivity (FC).

The DPARSF (http://rfmri.org/DPARSF) will be used to conduct fMRI data preprocessing[37] and the FSL tools (FMRIB Software Library) will be used to process T1WI structure data analysis [38]. The volumes of neocortical GM, total GM, and WM will be obtained by SIENAX (part of FSL 5.0)[39]. The normalized volumes of subcortical nuclei volumes will be estimated from FMRIB's integrated registration and segmentation tool (part of FSL 5.0, FMRIB Software Library)[40]. The cortical thickness will be obtained using FreeSurfer (http:// surfer. nmr. mgh. harva rd. edu).

Safety and adverse events

Every adverse event during the study will be timely recorded and reported by the safety officer. All potential risks during the study are listed on the participant's Informed Consent Form. All of them will complete an adverse effects questionnaire for TMS and MRI after intervention.

Availability of Data and Materials

The datasets will be generated and analyzed during the current study are available in the Clinical Trial Management, http://www.medresman.org. We will train all researchers which will record data in case report forms (CRFs) and sign them to ensure data quality. Any changes made on the CRF need to be indicated with a reason and date. Data collection and entry is performed by blinded and independent research assistants. Date storage will be in accordance with the protocols for maintaining security and privacy of data and will be protected by password.

Statistical analysis

Statistical analysis will be performed using IBM SPSS Statistics 25 (http://www.spss.com.hk). Intention-to-treat (ITT) analysis will be used to analyze the result which means the last observation will be used for interpolation when data missing. Continuous variables will be described as mean ± SD for normal distributions or median for non-normal distributions while categorical variables will be described as

frequency. For continuous variables that meet the assumptions of a normal distribution and homogeneity of variance, we will use the Two-way of variance with repeated measures; the Wilcoxon test will be used if not. A chi-square test will be used for categorical variables. Pearson correlation coefficient will be performed to detect the correlation between the primary outcomes (VAS, TQPEAK) and secondary outcomes (MEP, FC). When analyzing data obtained by repeated measurements, we will use two-tailed multivariate analysis of variance. The results will be considered statistically significant when the P value is less than 0.05. The post hoc comparisons will be performed by the Bonferroni correction for multiple comparisons if necessary.

Patient and public involvement

The researcher briefly explained the study content and asked the KOA patients for their agreement to share name and telephone number. The KOA patients, physiotherapists and orthopedic doctor took part in preparation of the proposal with face-to-face interviews. The recommendation of a health professional influences the decision on whether to take part in a program. Exit the experiment had no consequences for further treatment.

Discussion

KOA is classified as a peripheral joint disease, but changes of sensation-movement and pain are mediated by the central nervous system. Rasch et al[41]. proved that the muscle weakness caused by osteoarthritis is related to decreased joint function and increased pain, and that quadriceps training can increase muscle strength and relieve joint pain. Patients with KOA often exhibit strength deficiencies[1] and altered neuromuscular control[42] compared to those without KOA, which may result in suboptimal load dissipation within the knee. Though the motor output and pain changes resulting from KOA have been well-studied, the central contribution to muscle activity is less well known. In this protocol, we design four groups to prove the therapeutic role of high-frequency rTMS combined with quadriceps strength training compared to quadriceps strengthen training alone in KOA patients with 12-week intervention and explore changes of brain volume and function connection before and after treatment.

There are only two studies about to prove the treatment effect when combine noninvasive brain stimulation (tDCS) with exercise has been publicized [43, 44]. However, the design of the trial was inadequate, which used inappropriate randomization procedures had a small sample size. And the evaluation is only limited to the change of pain in KOA. Thus, we designed a stricter study to explore the dual clinical effects for reduce pain and muscle strength when the neuromodulation of the M1 with high-frequency rTMS combined with quadriceps strength training in KOA. In addition, to the best of our knowledge, this will be the first single-blind study on rTMS in KOA. Moreover, we will also analyze the correlation measurements between the primary outcomes (VAS, TQPEAK) and secondary outcomes (MEP, FC). Furthermore, the study’s exclusion criteria are relatively strict which will exclude many patients. In

this case, it is possible to ensure that our experimental results have a certain degree of accuracy and validity.

This research also has an inevitable limitation. The blinding cannot be performed for the participants and the study operator, because of the visible of the quadriceps strength training intervention, which might increase the risk of detection bias during the study's implementation.

In conclusion, the study will provide evidence to show whether there are synergistic effects following High-Frequency rTMS act on M1 combined with quadriceps strength training and clarify the brain mechanism of this therapeutic effect. The study will help provide rehabilitation prescription recommendations for people with KOA.

Study status

This trial is currently in the preparation phase. Participant recruitment will be started in October. 2023 and is expected to end in December.2023. The version of this protocol is the 1st version and the completion time in Feb. 2023

Abbreviations

KOA: Knee osteoarthritis; rTMS: repetitive transcranial magnetic stimulation; SPIRT: Standard Protocol Items for Randomized Trials; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; Rs-fMRI: Resting state functional MRI images; CRFs: case report forms; VAS: Visual analogue scale; KOOS: Knee Injury and Osteoarthritis Outcome Score; SF-36: 36-Item Short-Form Health Survey; MRI: Magnetic resonance imaging ITT: Intention-to-treat.

Declarations

Ethics approval and consent to participate

The present study has received ethical approval from the Ethics Committee of the Shanghai Seventh People's Hospital (2021-7th-HIRB-017). All participants will sign the informed consent to before the study and all methods will be performed in accordance with the Declaration of Helsinki.

Consent to publication

Not applicable

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

Ming-Hui Lai, Hai-Chen Xu have designed this trial protocol and draft ted the manuscript. Yu-Wu Ding, Kun Yang, Xue-Ping Xu and Li-Ming Jiang are part of the steering committee. They contributed to the development of methods, including participant recruitment, data collection and data analysis. All authors have read and approved the final manuscript.

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Figures

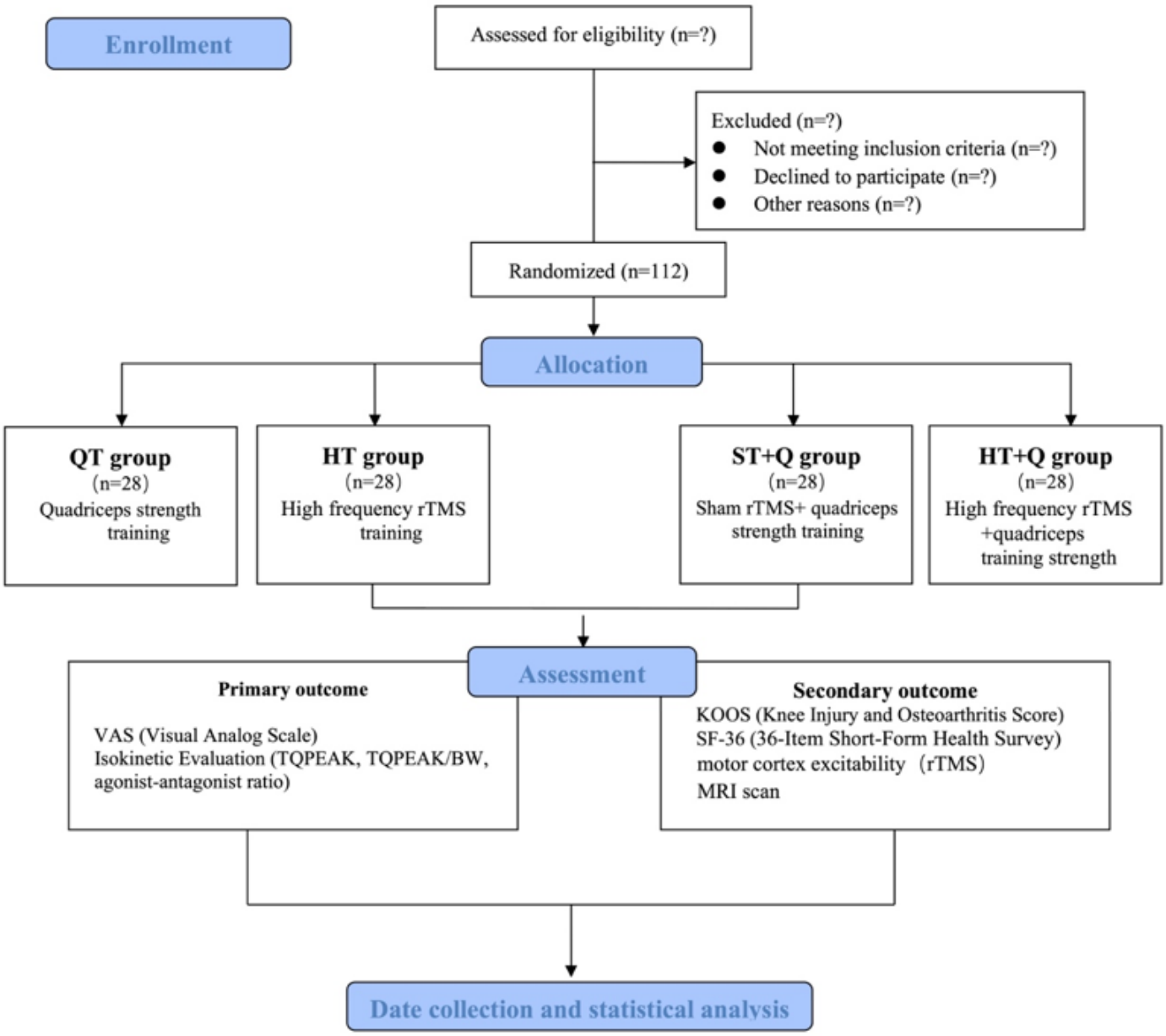

Figure 1

A brief flowchart of the entire study