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CLINICAL STUDY PROTOCOL

The Effect of Ankle Muscles Dry Needling on Brain Activity Map Based on fMRI: a Study Protocol for Randomized Controlled Trial

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Importance: Neuromodulation may be one of the underlying mechanisms of dry needling (DN); however, the mechanism has not yet been fully clarified.
Objective: This randomized controlled trial is designed to evaluate DN stimulation of the tibialis anterior and peroneus longus muscles in chronic ankle instability (CAI) and healthy subjects, employing functional magnetic resonance imaging (fMRI).
Design: Clinical study protocol, SPIRIT compliant.
Setting: Brain Mapping Laboratory.
Population: A total of thirty participants aged between 18 and 40 years old will be included in this study. Twenty healthy participants will be randomized into 2 groups (real DN and sham DN). Ten patients with CAI will also be recruited to the third group and receive only real DN for comparison.
Exposures: Real and sham DN.
Main Outcomes and Measures: The voxel count, coordinates of peak activation, and peak intensity will be obtained as primary outcomes to report brain map activation. Measurements will be taken before, during, and after DN treatment. The strength of the ankle dorsiflexors, active dorsiflexion range of motion, and McGill pain questionnaire short-form will be used as secondary outcome measures.
Results: The results from this study will be published in peer-reviewed journals and disseminated as presentations at national and international congresses.
Conclusion: This trial will explore brain responses to real and sham DN in healthy participants and to real DN in CAI patients. Overall, our results will provide preliminary evidence of the neural mechanism of DN.

Keywords: Chronic ankle instability, Dry needling, Functional magnetic resonance imaging, Ankle dorsiflexion

Trial registration: Iranian Registry Trial (IRCT): IRCT20210713051875N2.

INTRODUCTION

Dry needling (DN) is a common physiotherapy intervention that targets soft tissues [1,2]. DN has been used extensively in the treatment of myofascial trigger points, neuromuscular pain, scar tissue, and movement disorders [2]. The local mechanical effects of DN on central nervous system (CNS) modulations are considered physiological mechanisms [3]. Functional improvement in patients with neurological disorders after DN application has been reported in studies, suggesting that the CNS might be an important target of DN effects. However, there is currently no conclusive evidence about the neurophysiological aspects of DN effects [4-6]. Only one case study has investigated the effects of DN on brain activity using functional magnetic resonance imaging (fMRI), which demonstrated that one session of needle application increases activity in both the affected and unaffected primary motor cortex of a patient with stroke [7].

fMRI is one of the dominant neuroimaging techniques in the brain mapping field used to investigate homodynamic blood oxygenation level-dependent (BOLD) signals [8,9]. fMRI is a noninvasive, high spatial resolution method that can detect rapid changes in the neural activity of different brain regions [10]. Studies have investigated the effects of acupuncture stimulation on human brains with fMRI, revealing modulation in the somatosensory cortex, cognitive processing, and specific areas in the cerebellum. However, heterogeneity has been reported in the studies, and thus, conducting more high-quality studies has been highlighted [9,11]. In addition, to the best of our knowledge, no clinical trial has compared brain activity simultaneously with movement tasks before and after needle application.

Chronic ankle instability (CAI) is one of the most common musculoskeletal disorders [12]. It has been suggested that deficits in the cerebellum are associated with ankle instability [13]. Shen et al. (2022) showed that CAI patients have less functional connectivity between hemispheres, which can lead to less functional synergy [14]. However, these studies have investigated brain mapping under static conditions (rest-fMRI) [13,14]. DN application to the tibialis anterior and peroneus longus muscles in patients with CAI has been shown to improve neuromuscular and static postural control, the positive effects of which might be explained by central mechanisms and improvements in descending cortical output [15,16]. Task-fMRI, including dorsiflexion movement, is a valid method for investigating cortical and subcortical circuits [17]. Therefore, we designed a study to use task-fMRI to explore and compare the possible effects of DN on brain activation maps in healthy subjects and patients with CAI during active ankle dorsiflexion. We also aimed to assess the brain activation map during DN application.

MATERIALS AND METHODS

1. Study design

This study is a parallel randomized controlled trial. The study will include 3 groups. Twenty healthy participants will be randomized to 1:1 groups: 1) the real DN group and 2) the sham DN group. Ten patients with CAI composed the third group, and real DN will be applied as an intervention. All procedures will be conducted in accordance with the Ethical Committee of Tehran University of Medical Sciences (TUMS) (Code: IR.TUMS.FNM.REC.1401.115), and participants will be asked to provide written informed consent. The overall schedule is shown in Table 1.

2. Study population

Eligible participants will be recruited from November 2023 to March 2024.

1) Inclusion criteria

1. Age: 18-40 years.
2. Participation in sports or physical activities based on the Baecke questionnaire (a score of 8 or less).

Table 1. SPRIT study period for various stages of the study

Time point	Study period				
	Enrollment	Allocation	Post-allocation		
	$-t_1$	t_0	t_1	t_2	t_3
Enrollment					
Eligibility assessments	×				
Demographic questionnaire	×				
Informed consent	×				
Allocation		×			
Interventions					
Dry needling				×	
Sham needling				×	
Assessments					
Dorsiflexion active range of motion		×			×
Dorsi flexor strength		×			×
McGill pain Questionnaire Short-form		×			×
fMRI scan					
Dorsi-flexion tasks			×		×
Dry needling paradigms				×	

SPRIT = Standard Protocol Items: Recommendations for Intervention Trials; $-t_1$ = pre-study, screening/consent; t_0 = pre-study, Baseline/randomization; t_1 = study, before intervention; t_2 = study, intervention; t_3 = study, immediately after intervention.

3. The dominant leg is the right leg.
4. Subjects with right CAI should have the following criteria:
   a. History of recurrent sprain in the right ankle, with at least one ankle sprain in the past 6 months.
   b. Ankle sprain accompanied by signs of inflammation and limited daily activity for at least one day.
   c. Experience at least 2 episodes of giving way in the 6 months preceding the study.

Ankle instability will be diagnosed using a self-administered Cumberland Ankle Instability Tool questionnaire.

2) Exclusion criteria

1. Any history of neurological or cardiovascular diseases.
2. Musculoskeletal disorders in lower limb joints other than the ankle in patients with ankle instability and any musculoskeletal disorders in the lower limbs in healthy participants.
3. Medical conditions during scanning, including headaches.
4. Drug or alcohol abuse.
5. Any contraindication to DN.
6. Contraindications to MRI (e.g., pacemakers).

3. Randomization and blinding

The assessors and data analysts will be blinded to the allocation groups. Healthy subjects will not be informed about the differences in interventions between the two groups. The physiotherapist who will perform the treatments will be blinded to the assessments. Concealment of allocation will be completed by the sequentially numbered opaque sealed envelope (SNOSE) technique [18].

4. Intervention

Subjects in each group will receive one DN session. An experienced and licensed physiotherapist will deliver DN to the tibialis anterior and peroneus longus muscles. Sterilized stainless needles (0.25 × 30 mm; SMC, Seoul, Korea) using a fast-in and fast-out cone-shaped method will be used [4]. The points approximately near the motor point locations will be needled for each muscle [2]. The tibialis anterior will be needled one centimeter lateral to the point at 1/3 and 2/3 of a straight line from the tibial tuberosity to the medial maleole (Fig. 1A) [19]; this point matches the stomach ST37 acupuncture point [20]. The peroneus longus will be needled at a point at 1/4 and 3/4 of an imaginary line between the fibular head and lateral maleole (Fig. 1B) [21], which is located between the acupuncture points of gallbladder GB34 and GB35 [20]. The sham DN will be delivered at the aforementioned points via a monofilament (4 cm; GIMA, Italy) [9,22].

5. Outcome measures

The demographics of the participants, including age, sex, and body mass index, will be recorded at the baseline assessment. The details of the primary outcome assessment will be clarified in the following. Secondary outcomes will be measured before and immediately after the fMRI scanning session.

1) Primary outcomes

The primary outcome will be acquired using a 3.0 Tesla magnetic field (Siemens, MAGNETOM Prisma) via a standard 20-channel head coil. High-resolution T1 images will be obtained with the following parameters: repetition time (ms): 2,000, echo time (ms): 3.47, flip angle: 7°, slice thickness (mm): 1, number of slices: 176, and matrix size: 256 × 256. The fMRI parameters for the scan are as follows: repetition time (ms): 2,000, echo time (ms): 30, flip angle: 80°, slice thickness (mm): 3, number of slices: 48, and matrix size: 64 × 64.

fMRI measurements will be performed before, during, and after DN intervention. A brain activation map will be generated, and the number of voxels activated, coordinates of peak activation, and peak intensity will be reported.

Task fMRI will be completed by using a block design. Dorsiflexion tasks will be performed in 2 separate phases before and after DN, and each phase will contain 5 blocks

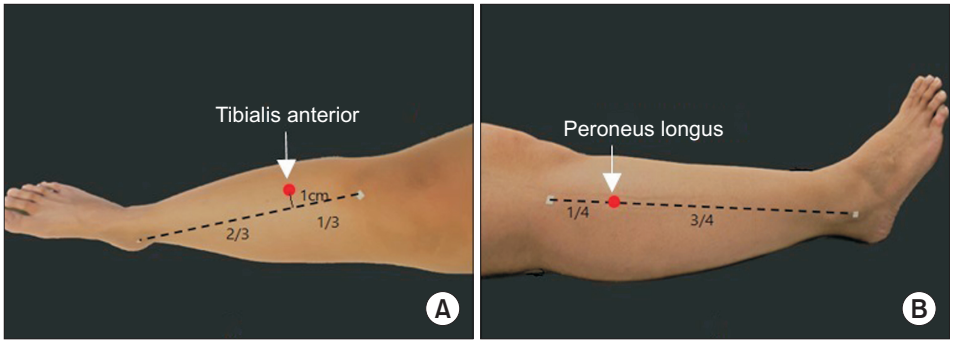

Fig. 1. Points for dry needling of (A) tibialis anterior (B) peroneus longus.

(20 seconds) of 8 active dorsiflexion repetitions alternating with rest periods. The subjects will be asked to perform dorsiflexion movements in response to visual feedback. DN intervention will be applied between ankle dorsiflexion paradigms. Four blocks (30 seconds) with rest between each block will be allocated to the tibialis anterior, and another 4 blocks will be devoted to the peroneus longus.

2) Secondary outcomes

The strength of the ankle dorsi flexor muscles will be measured by a standard manual dynamometer (Micro Manual Muscle Tester; North Coast Medical, Inc., USA). The reliability and validity of manual dynamometry have been previously established [23]. The subjects will be asked to sit in an erect position with the hip and knee in 90° flexion while their heel will be kept on the ground during the test. The dynamometer pad will be placed on the base of the metatarsals, and the subject will be instructed to dorsiflex the foot for 10 degrees and maintain maximal effort against the dynamometer pad for 5 seconds [24]. Three tests with a one-minute rest period between them will be performed, and the best results will be reported in Newton.

The degree of active range of motion of ankle flexor dorsiflexions will be assessed by a standard goniometer. The assessment will be conducted based on methods described in previous studies [25].

Pain will be measured in people with CAI using the Persian version of the McGill Pain Questionnaire Short-form [26]. The total pain score is calculated by summing all the individual scores.

6. Data monitoring

An independent team from different disciplines at the National Brain Mapping Lab (NBML), including a physician, will constantly monitor the data acquisition methodology to ensure participant safety. An independent committee will evaluate the data.

7. Statistical analysis

Statistical analysis will be performed with SPSS version 20.00 (IBM, NY). The normality of the data will be checked using the Kolmogorov-Smirnov test. The mean and standard deviation will be calculated for continuous variables. Differences in baseline characteristics among the three groups will be assessed by one-way analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test. Mixed-design repeated-measures ANOVA will be used to determine the main effects and interaction effects. The Bonferroni correction will be used for multiple comparisons. When the variances are not equal, as revealed by Mauchley's test, the Greenhouse-Geisser correction will be applied. The non-parametric Friedman test will determine the differences among groups if the data are not normally distributed. A post hoc Wilcoxon signed-rank test (WSRT) will be used for multiple comparisons within groups, and the differences between groups will be analyzed using the Kruskal-Wallis test. A paired t-test will be used to compare the pain levels before and after treatment within the patient group to determine whether there is a statistically significant improvement. When the pain data is not normally distributed, the non-parametric WSRT will be used. The effect sizes will be calculated with Cohen's d and interpreted as follows: negligible (< 0.20), small (between ≥ 0.20 and < 0.50), moderate (between ≥ 0.50 and < 0.80), and large (≥ 0.80). A p-value of less than 5% will be considered statistically significant.

1) fMRI data analysis

fMRI data analysis will be performed using statistical parametric mapping (SPM12) software. The preprocessing steps were as follows: field map correction, motion correction, co-registration of functional and anatomical images, realignment, slice timing, normalization, and smoothing.

Dorsi-flexion (pre-needling) vs. rest, Dorsi-flexion (post-needling) vs. rest, DN vs. rest, and Dorsi-flexion (pre-needling) vs. Dorsi-flexion (post-needling) will be defined as contrasts for extraction of the brain activation maps- first-level analysis will be conducted by applying a general linear model (GLM) to obtain brain map activation for each subject. ANOVA will be used for group-level analysis to demonstrate differences among the groups.

DISCUSSION

Few studies have investigated the effects of DN on brain activity [7,27,28]. The effects of DN on the brain remain unknown. To the best of our knowledge, this is the first study designed to explore the central mechanisms of DN using fMRI. This trial will allow us to investigate brain activity before, during, and after DN application.

The possible effects of DN could be explained by complex mechanisms. However, these underlying mechanisms are not yet fully understood [29]. The effects of DN may be explained by mechanical disruptions and sarcomere lengthening, resulting in a reduction in the overlap of actin and myosin and alterations in the neuromuscular junction response. Furthermore, reductions in peripheral nociception, dorsal horn neural activity modulation, and stimulation of Aδ and C fibers have been suggested as neurophysiological mechanisms [30,31]. Recent studies have shown correlations between peripheral lesions (e.g., CIA, carpal tunnel syndrome) and central pathological mechanisms [13,14,22]. Therefore, it may

be hypothesized that successful DN treatment may alter brain activity, playing an important role in clinical improvements after DN.

The potential strength of this study is that brain activation maps in CAI patients will be explored compared to those in healthy controls, and we will also control for the somatosensory effects of the real DN compared to those of the sham DN. The primary limitation is that we will evaluate the short-term effects of DN on brain activation maps. Further studies should be performed to assess the possible long-term effects of DN.

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AUTHORS' CONTRIBUTIONS

SN, NNA, JD and RH conceptualized the study. SN, NNA, and RH contributed significantly to design and methodology of the study. RH wrote the first draft of the manuscript which was revised for critically intellectual content by NNA, SN, and JD. All authors read and approved the final manuscript for submission.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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