Study Protocol and Statistical Analysis Plan

Title of Study: The Effect of Graded Motor Imagery on Pain and Function in Individuals with Knee Osteoarthritis: a Comparative Randomized Controlled Trial
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Study Protocol

Objectives:

The objective of this study was to investigate whether Graded Motor Imagery (GMI) shows comparable effectiveness to Transcutaneous Electrical Nerve Stimulation (TENS) in improving pain and functionality in individuals diagnosed with knee osteoarthritis (PwKOA).

Design:

A small randomized controlled trial design was conducted online at three time points: 1) baseline/pre-test, 2) post-test (after the 8-week intervention), and 3) follow-up (6-week follow-up). Data were collected by face-to-face interview method.

Participants will be randomly assigned to one of two conditions: 1) GMI or 2) TENS. One group underwent GMI treatment, while the other group received TENS therapy three times a week for 8 weeks. Additionally, both groups engaged in home-based and functional exercises.

The study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (date: 02/06/2023, procedure number: 09.2023.795) and was by the ethical standards of the World Medical Association (Declaration of Helsinki).

Methods:

Sample and Recruitment. Patients diagnosed with unilateral knee osteoarthritis (KOA) were included in the study. To participate in the research, the following criteria must be met: 1) Grade II-III KOA as per the Kellgren and Lawrence classification and American College of Rheumatology (ACR) criteria, accompanied by symptoms and radiographic evidence; 2) experience moderate to severe pain rated as three or higher on the Visual Analog Scale (VAS) during activity; 3) participants must score at least 24 points on the Mini-Mental State Examination (MMSE); 4) age of the participants should be between 45 and 64 years. Patients diagnosed by an orthopedist were treated by a certified physiotherapist at Artvin State Hospital between 1 July 2023 and 31 March 2024.

Procedure. Throughout the GMI protocol, participants engaged in three weeks of lateralization, followed by three weeks of motor imagery (MI), and concluded with two weeks of mirror therapy (MT). Lateralisation training was conducted using the Recognise™ Knee app. The four-stage program included 20 different knee images in each stage, with a viewing time of 5 seconds, progressing from easy to difficult (Basic, Vanilla, Context, and Abstract). During the MI task, subjects were instructed to mentally simulate engaging in activities such as climbing, swimming, and gardening. During the implementation of MT, a 90×60 cm^2 mirror is positioned between the lower extremities of seated patients. Subsequently, patients engage in active and progressive resistance exercises for the unaffected knee while maintaining the affected knee in a stationary position. As patients progressed, they engaged in active and progressive resistance exercises targeting the affected knee up to their pain threshold. Ultimately, they attained an equal range of motion (ROM) and resistance in both extremities. The TENS therapy was administered under medical supervision using the Intellect device by Chattanooga Group in Hixson, TN, and four distinct self-adhesive electrodes (5.08 × 5.08 cm, Uni-Patch, Wabasha, MN). The electrodes were placed in a square shape over the area of pain. Conventional TENS was used for 30 minutes at 100 Hz frequency, with a 100 μs pulse width,

and intensity kept below 10% of the motor threshold. The exercise program included warm-up, core stability, pelvis and hip stability, gluteus medius strengthening, knee control and stability, knee strengthening exercises, and functional exercises. The home exercise protocol consisted of a 10-minute warm-up with walking, followed by stretches and exercises including straight leg raises, quadriceps setting, pillow squeezes, heel raises, one leg balance, step-ups, and quadriceps strengthening exercises, each performed in three sets of ten repetitions with a 3-minute rest in between sets.

Measures. All measurements were collected at baseline, after treatment, and during the 6-week follow-up for both groups. The only exceptions were sociodemographic characteristics and mental status, which were only assessed before the treatment began.

Mini-mental state examination (MMSE). The 11-question Mini-Mental State Examination (MMSE) with a maximum score of 30 was used for cognitive assessment. A score of 24-30 indicates normal cognitive function, while a score of 18-23 suggests mild dementia, and a score of 17 or lower indicates severe dementia.

Visual analog scale (VAS). Pain severity was measured using the Visual Analog Scale (VAS). Patients used a 10 cm VAS scale to indicate the severity of pain at rest, during activity, and at night, on a scale from 0 (no pain) to 10 (unbearable pain). Pain levels were categorized as 0-2 (safe), 3-5 (acceptable), and 6-10 (risky).

Pressure pain threshold (PPT). PPT was measured using an algometer model 1200–304(Push-Pull Force Gauge®, Fabrication Enterprises, Inc.). The evaluation was performed at points located 2 cm below the medial and lateral edges of the patella with patients lying on their side. The algometer applied gradual pressure until pain was reported. Each point was tested three times, and the average value was calculated. This method and device are reliable for PwKOA.

Range of motion (ROM). Knee flexion and extension was measured in the prone position using a digital goniometer (Baseline Evaluation Instrument® by Fabrication Enterprises, Inc.). The evaluation was conducted with the pivot point at the femur's lateral condyle. The stationary arm tracked the lateral midline of the femur, whereas the moving arm followed the fibulaThe measurements were performed three times, with a 30-second interval between tests, and the most accurate value was recorded.

Isometric muscle strength. Isometric muscle strength for knee flexors and extensors was assessed using a handheld dynamometer (MicroFET 2, Hoggan Health Industries Inc., Biometrics, The Netherlands). Measurements were taken three times with 30-second intervals in between. The average value in kilograms was recorded. Patients were positioned on the edge of the bed with an upright posture, arms crossed, and hips and knees flexed at a 90° angle. The dynamometer was placed two finger-widths above the lateral malleolus on both the anterior and posterior aspects of the tibia.

Timed up and go test (TUG). The physical performance was assessed with TUG in PwKOA by timing the process of standing up from a chair, walking along a line, turning, and sitting back down. The average time of two trials is calculated after the initial attempt.

Western Ontario and McMaster Universities osteoarthritis index (WOMAC). The assessment of pain, stiffness, and physical function was carried out using the WOMAC, which encompasses 24 items scored on a scale ranging from 0 to 4. Elevated scores are indicative of heightened disability.

Statistical Analysis Plan

Statistical analysis was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Qualitative variables were expressed as frequencies and percentages, whereas quantitative variables were presented as means and standard deviations. The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. Homogeneous

numerical variables were compared using the Independent Samples T-Test, and categorical variables were analyzed using the Chi-Square Test to assess pre-treatment demographic characteristics between groups. Repeated measures ANOVA (rANOVA) was employed to compare baseline (T0), post-treatment (T1), and six-month follow-up (T2) scores, with Bonferroni post hoc analysis conducted to identify the specific sources of differences. A mixed between-within subjects analysis of variance with Tukey's post hoc test was utilized to evaluate the effects of two different treatments (GMI, TENS) across three time points (baseline, post-treatment, and six-month follow-up). In all analyses, statistical significance was set at $p<0.05$ (two-tailed).