Study Protocol Document Cover Page

Official Title of the Study: Trial of Self-managed Approaches for Patellofemoral Pain Syndrome in Active Duty Military

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Trial of Self-managed Approaches for Patellofemoral Pain Syndrome in Active Duty

Objective

The overall objective of this project is to compare the three home-managed treatment regimens for PFPS: neuromuscular electrical stimulation (NMES), transcutaneous electrical nerve stimulation (TENS), and NMES combined with TENS to a standard home exercise program (HEP). Each of the three treatment arms will be supplemented by HEP and compared to a group receiving standard HEP alone. Our central hypothesis is that the combination of NMES with TENS will show significantly greater improvements in muscle strength, mobility, pain, daily activity and quality of life (QOL) than HEP alone.

Design

The Study will use a two-by-two factorial (NMES +/- and TENS +/-) design with repeated measures over time to compare the effects of NMES, TENS and combined NMES/ TENS on strength, mobility, symptoms, and QOL on military members with PFPS to the effects of a standard home exercise program. All groups will participate in the standard home exercise protocol. The groups will be assessed over 9 weeks to compare main and interactive effects over time. All groups will have an intensive 9-week program.

Participants will be randomly assigned to 1) NMES with the standard HEP protocol; 2) TENS with standard HEP protocol; 3) NMES and TENS with standard HEP protocol; and 4) standard HEP protocol alone (control group). We will not randomize participants until after the pre-treatment assessment has been completed. Participants will be familiarized with the test procedures prior to baseline testing, and then assessed again at 3, 6 and 9 weeks. The primary outcome measures are lower extremity muscle strength, physical activity, and mobility; and the secondary measures are symptoms/pain and QOL.

Methods

Intervention: The rationale for the number of weeks of intervention and the number and timing of assessments is based on our previous work. NMES was found to increase strength after 36 sessions of training22. We will test participants at baseline, 3-weeks, 6-weeks, and 9-weeks when all outcome measures will be tested. Subjects in the NMES groups will have their percentage of MVC calculated to adjust the intensity of their NMES training. Information on pain status will be obtained at weekly checks, regardless of group assignment. The intervention weekly logs to determine pain and difficulty during home exercise, NMES and TENS will be reviewed and adjusted, as necessary. We will have weekly contact with participants during the 9 weeks of the study (baseline – week 9) either by in-person clinic visits, phone checks, text messaging or email.

The Control Home Exercise Program (HEP) Protocol: All participants will receive a standard home-based exercise rehabilitation protocol for PFPS. HEP teaches muscle strengthening exercises and self-management strategies to prevent recurrence. The HEP sessions provide the participant with a self-management framework for returning to duty following PFPS rehabilitation. During their baseline visit, participants will be provided a handout and given a demonstration of the daily exercises to be performed at home. A return demonstration by the participant will assure understanding. The exercises are quadriceps strengthening exercises. These exercises consist of stretching exercises of the quadriceps and hamstring muscles and a combination of open chain and closed chain exercises. The combined open and closed chain exercises are active straight leg raises, quadriceps straightening, step

up, and squats. At each study visit, participants will receive instructions on self-management strategies to prevent recurrence. The study coordinator will coordinate all study visits regardless of group assignment. Follow-up telephone calls will be made to remind participants of their visit and to control for individual contact made through phone calls to participants in the intervention group. To provide an attention control, the HEP only group will receive weekly communication from the study coordinator regarding compliance with the exercises. Delivery of the interventions for each arm of the study will be conducted independently, so there will be no cross-contamination between groups. The HEP group will receive a total of 62 sessions.

Self-Managed Neuromuscular Electrostimulation (NMES) Program: : The two NMES treatment groups will receive a portable battery-operated device, KneeHAB® XP (Bio-Medical Research, Galway, Ireland) with the thigh garment [43]. This device is FDA approved. The unit is powered by a 3.6V NiMH rechargeable battery pack. A battery charger is included with the unit. NMES training will consist of 20-minute stimulation sessions performed concurrently with the Home Exercise Program (HEP) for 9 weeks; each 20-minute NMES. NMES with the thigh garment will be used as the participant is performing the home exercises of stretching followed by the combined open and closed chain exercises. Those in the NMES group will alternate HEP alone and NMES with HEP for a total of 62 sessions (31 sessions of NMES/HEP and 31 sessions HEP alone).

KneeHAB® XP generates coordinated muscle contractions using a patented stimulation system called "Multipath". This approach changes the current pathways between the electrodes for preset periods within each pulse, thus allowing multiple pathways for current flow. This method, compared to conventional NMES, allows for higher stimulation intensities that maximizes muscle fibre recruitment producing stronger muscle contractions while minimizing muscle fatigue [44].

This dual channel device delivers a pre-set program of NMES using a symmetrical square biphasic waveform with an output current in the range of 0-70 mA. Parameters for the work cycle of the NMES unit will be variable pulse duration of 300-400 μs; a ramp time of 1.0:0.50 seconds; frequency of 50 Hz; contraction time of 5 seconds on and relaxation time of 10 seconds off. The total cycle length is 16.5 sec. This provided a total ON time of 6.06 min in each 20 min session.

The KneeHAB® XP Thigh Garment [45] (see Figure 2) provides proper thigh electrode placement built into the specialized wrap to ensure accurate application. It is a light-weight, breathable fabric that wraps around the thigh with precise placements of the 4 electrodes (A, 10 X 20 cm; B, 3 X 18 cm; C, 10 X 7.5 cm; D, 7 X 14 cm.) over the quadriceps muscles (vasti and rectus femoris muscles) of the affected leg. The electrodes are self-adhering reusable hydrogel electrodes (Neurotech®, Galaway, Ireland).

To ensure consistent interventions across participants, a specified percentage of baseline maximal voluntary contraction (% MVC) will be used to determine the intensity of the training contraction. The electrical amplitude to obtain the desired intensity will be determined for each participant. Participants will train at 20-30% of MVC during weeks 1-3, 30-40% of MVC during weeks 3-6, and 40-50% of MVC during weeks 6-9. Incremental increases will be made at the 3- and 6-week clinic visits. Individualized instructions for adjusting the amplitude dial settings, with a return demonstration, will be used to maintain the appropriate percentage of MVC. During the home training sessions, participants will adjust the amplitude required to achieve the desired goal, as tolerated. The first 5 minutes of each study visit will be used to review training logs, determine if NMES goals were achieved and troubleshoot any problems.

Self-Managed Transcutaneous Electrical Nerve (TENS) Program: The TENS treatment groups will receive the battery-operated KneeHAB® XP [43] with lead wire TENS applicator. The TENS protocol consists

of 20-minutes of TENS stimulation while concurrently performing the HEP. The TENS with HEP and HEP alone will be alternated for 9 weeks for a total of 31 TENS/HEP sessions and 31 HEP alone for a total of 62 sessions. The TENS stimulation parameters of the machine are fixed by the manufacturer. The KneeHAB® XP delivers a pre-set program of pulsed electrostimulation using a symmetrical square biphasic asynchronous, frequency modulated waveform. Parameters for the TENS unit will be pulse duration of 200 μs; Frequency is at 99 Hz. Short electrical pulses are sent via reusable self-adhesive conductive gel pads to the surface of the skin. and The KneeHAB® XP with TENS applicator uses four 2" (5cm) round StimTrod™ electrodes (Axelgaard, Fallbrook, CA) that are self-adhering and reusable. Electrode placement is around the knee with the lead wires attaching to the electrodes using a criss-cross technique.

Combined Self-Managed NMES and TENS Program: The combined NMES/TENS treatment group will receive the KneeHAB® XP with the thigh garment and lead wire TENS applicator. The same parameters for TENS and NMES will be used (described above). The NMES and the TENS protocol will be performed on alternating days. There will be a total of 31 NMES sessions with HEP and 31 TENS sessions with HEP for a total of 62 sessions.

Adherence to NMES and TENS Protocols**:** Adherence to the protocol will be ascertained by having participants complete daily training logs with the date, time, amplitude dial setting used during stimulation, and pain status. The KneeHAB® XP controller has a compliance monitor that records the intensity level, average intensity level over 4 sessions and the total amount of time the stimulator was used. This time will be compared to the NMES training logs.

Data collection: Variables and Their Measurement

Clinical and Demographic Variables: Information will be collected on age, sex, co-morbidities, medication use, use of assistive aids, symptom duration, history of

injuries/trauma, changes in frequency, duration and intensity of training, previous surgeries, imaging studies and other self-care methods currently being used to improve pain and/or mobility. Height and weight will be measured without shoes with the head held horizontal and chin parallel to the floor while standing on a flat surface using a calibrated balance beam scale and stadiometer; they will be used to calculate body mass index (BMI: weight in kg divided by square of height in meters). Resting blood pressure (B/P) will be measured in triplicate in a seated position. The lowest of three blood pressure measurements will be recorded. Resting heart rate will be measured using the radial pulse over 1 minute's duration.

The amount of lower extremity fatness dampens the amount of electrical current reaching the muscle, potentially affecting the strength of the contraction. Therefore, we will measure thigh fatness, skinfold measures and thigh circumference will be obtained. First, the subject will stand so that 4 cm distal to the midpoint of the right thigh (distance halfway between the greater trochanter and lateral epicondyle) can be marked with an indelible pen to determine where the circumference and skinfold measurements are made. The subject will then be placed in the supine position on a table, with the right foot on the table surface and the knee at about a 90° angle. Total thigh circumference will be measured using a fiberglass tape (Gulick, Country Technology, Gay Mills, WI). Skinfold will be measured using calipers (Lange Skinfold Calipers, Country Technology, Gay Mills, WI), with both a low spring tension (measured at 5 g at the opening of the caliper) and a normal spring tension (measured at 26 g at the opening of the caliper). To obtain the skinfold, the skin will be grasped between the thumb and index

finger above the marked location, such that the fold is along the long axis of the leg. The caliper will then be applied 1 cm below and at right angles to the pinch to obtain a skinfold measure. When the same person performs these measures on different days, the coefficient of variation is less than 5%. We will use one person to perform each measure to ensure reliability and avoid contamination by inter-tester variability.

Outcome Measures: The primary measures to be studied are lower extremity muscle strength, physical activity, and mobility; secondary measures are symptoms of PFPS and QOL.

Assessment of Lower Extremity Muscle Strength: The strength of knee flexion and extension muscle groups will be measured using the Nicholas Manual Muscle Tester (MMT) (Lafayette Instrument Company, Lafayette, Indiana), a handheld device which measures knee extensor (KE) and flexor (KF) muscle strength as described by Dunn and Iversen. The participant will be positioned with a small towel roll placed distally to support the femur in 90-degree hip flexion. The participant's knee will be placed in 70º knee flexion using a goniometer. The distance from the tibial tuberosity (TT) to the superior aspect of the medial malleolus will be measured.

Three locations (per limb) for the strength measurement will be taken using the MMT. To assess knee extension, the first measurement will be 5 cm distal to TT on the anterior limb. To assess knee flexion, the second measurement will be 5 cm distal to TT on the posterior limb. The third measurement will be the standard protocol for the MMT (distance from the tibial tuberosity to the superior aspect of the medial malleolus, multiplying by 0.6); this measurement will be used as a standard normative reference for strength comparisons to other populations. Each participant's muscle groups will be tested in the following order: right knee extensors (RKE), right knee flexors (RKF), left knee extensors (LKE), left knee flexors (LKF).

For each test, participants will perform three maximal efforts holding each contraction for 4 seconds, separated by 30-second rest; the highest value of the three trials will be accepted in kilograms. Reliability of the NMMT was determined by using 1-day repeat testing with intrarater correlation coefficients ranging from .97 to .99 50. Pearson correlation coefficients between the NMMT and a Cybex II dynamometer ranged from .64 to .76 50.

Assessment of Mobility and Physical Activity: Mobility will be measured by these procedures: a timed stair climb, step down test, timed chair rise test and a 6-minute walk test. Additional physical activity measures will be the monitoring of steps walked and energy expenditure.

The Timed Stair Climb Test will test the functional activity of stair climbing. The test will begin with participants ascending up four steps (6-inch rise, 11.5-inch run) to a 30-inchsquare platform, and then descending to the bottom of the stairs. Participants will climb the stairs at a self-selected pace using the handrails if necessary. Each participant will complete two complete rounds, if possible, and the two times will be averaged to produce one score. Performance-based measures such as the stair climb have high test-retest reliability and are inversely correlated to quadriceps muscle strength and cardiovascular capacity. After completing the test, a visual analog scale (VAS) for pain will be administered to quantify pain during the effort.

The Forward Step-Down Test is a specific function test for PFPS, putting weight bearing stress during a movement that mimics stair descent. The test is performed from a 20 cm (8 inch) high platform.

The participant steps forward and down toward the floor from a single-leg stance with a straight knee (hands on hips). The knee of the stance leg bends until the opposite foot lightly touches the floor with the heel and then returns to full knee extension. The heel touching the floor is not to be used to accelerate back onto the platform. This counts as one repetition; the number of repetitions performed in 30 seconds is recorded. Both legs are tested separately. The intraclass correlation coefficient for the step-down test reliability was 0.94 with standard error of the mean 0.5354. The correlation coefficient between the step-down test and the VAS for pain was 0.57 ($p<0.01$)54.

The 30-Second Chair Stand Test assesses lower-body strength mimicking squatting. The participant completes as many full stands as possible in 30 seconds. The participant sits in the middle of the chair, feet flat on the floor with arms crossed at the wrists and held against the chest. When instructed, the participant rises to a full stand, and then returns to a fully seated position. The number of completed rises will be recorded. The correlation coefficients of chair stand test scores to leg press (1RM) scores was r=0.68.

The 6-Minute Walk Test (6-MWT) measures the distance a participant walks at a “fast” pace over a 6-minute period. Participants will “walk as quickly as you can” with the opportunity to stop and rest if required. This test measures functional capacity of walking. Normal reference for healthy adults on the 6-min walk distance has been published. The 6-MWT has demonstrated submaximal exercise at 72.7% +/- 11.6% of V̇O2max. with rank order correlation of 0.49 (P = 0.001) between 6-MWT and V̇ O2max. Test-retest reliability was ICC = 0.917 [0.862-0.951]).

Mobility: Physical Activity Measures: Physical activity will be measured using the Fitbit Charge (San Francisco, CA). The Charge is a wrist-worn three-axis accelerometer that measures steps walked, distance traveled, energy expenditure and floors climbed. The frequency, duration, intensity and patterns of movement are recorded. The unique feature of this device is a wireless function that automatically uploads data to designated mobile phone devices or computers. Batteries are rechargeable and last 5-7 days. Fitbit products use similar accelerometry for all their products. Thus, we assume that each of their products have similar validity and reliability. In our personal experience comparing the Charge to the Jawbone and the well validated Digiwalker, we found very similar accuracy of steps. Fitbit devices have been shown to be reliable and valid when compared to standard research-grade devices for energy expenditure (r=0.89-0.97). Fitbit accuracy estimates report 10% error (90% CI) for energy expenditure compared to a portable metabolic system. In the current study, baseline data will be ascertained by wearing the Charge for 3 days while maintaining a typical activity pattern. Subsequently, the device will be worn daily for 9 weeks.

Assessment of Symptoms of Patellofemoral Pain Syndrome: Pain associated with activity limitations will be measured by the Kujala Anterior Knee Pain Scale 64, a 13-item knee specific self-report questionnaire. Scores range from 0 to 100 with higher scores indicating better performance. In patients with anterior knee pain, high test-retest reliability was demonstrated over 2-3 days (ICC=0.95), with moderate change score correlations (r=0.42).

Knee Injury and disability will be measured by the International Knee Documentation Committee (IKDC) subjective knee form, a well standardized outcomes questionnaire that is knee-specific and assesses patients with various knee disorders66. The 18-item instrument assesses symptoms, function and level of sports participation for those with an injured knee. The IKDC subjective knee form has demonstrated reliability, construct and concurrent validity and responsiveness.

The Visual Analog Scale (VAS) of pain will be used to assess pain at rest and after activity. Participants will complete this scale following the stair climb, step down test, 6-minute walk and the chair rise test. This VAS pain subscale is a 100-mm horizontal line index with descriptive anchors at each end. At the far left (0.0 cm) is "no pain" and at the far right (10 cm) is "worst possible pain". The participant is instructed to place a vertical line at some point between the anchors to describe his/her level of pain. The VAS pain scale shows high correlations with acute pain levels.

Assessment of Quality of Life (QOL): The SF-12v2 Health Survey® (SF-12) will be used to determine each participant's overall health-related quality of life. This widely used multidimensional scale has two summary scores for physical and mental health as well as eight subscale scores. The SF-12® is a shorter version of the SF 36® and contains 12 items**.** It has been validated in patients with a variety of orthopedic conditions and in athletic patients. Internal consistency of the SF-12 component summary scores are ≥0.82 for the physical component summary (PCS) scale and 0.75 for the mental component summary (MCS) scale (Cronbach's alpha). Mean scores for the SF12 PCS and MCS were similar to the SF 36.

In addition, depressive symptoms will be measured by the Centers for Epidemiologic Studies Depression instrument, a self-administered questionnaire that contains 20 items. The CES-D shows excellent internal consistency (coefficient alpha >0.85) and test-retest correlations (r >0.5).

Compliance/Adherence to Treatments: Compliance/adherence to the interventions will be measured at multiple levels. Adherence to the standard HEP rehabilitation protocol, TENS and NMES will be computed as the number of home sessions reported on the participant's log divided by the total number of sessions prescribed (daily). Adherence to NMES intensity training (stimulating at the prescribed % of MVC) will be defined as the number of sessions achieving the monthly goal divided by the number of sessions prescribed. Individual NMES and TENS reliability will be assessed from the total stimulation time recorded in the stimulator compliance monitor and by cross checking with training logs in which participants record their daily stimulation time.

Study population:

To obtain a sample size of 136 adults with PFPS (34 per group), we will draw upon Active Duty members and Reserve/National Guard members on active duty status through the physical therapy clinic, family practice clinic and satellite clinics at BACH. All racial, ethnic, and gender groups will be recruited for the study. Active duty members who meet eligibility criteria and agree to participate in the study will be asked to participate.

The number of visits required for participants in all groups is 4, including 1 baseline visit, 2 visits for education and strength adjustments, and testing (weeks 3 and 6) and 1 9-week post-test assessment visit, for a total of 4 visits. The 3, 6, and 9-week visits will include strength adjustment, review of logs and abbreviated testing. Each standard BACH rehabilitation session will take 20 minutes, and each assessment (Weeks 3, 6, 9) approximately 1 hour and 10 minutes, with baseline testing 2 hour and 10 minutes; the total time over the 9 weeks will be approximately 5 hours and 45 minutes (Table 3).

Inclusion Criteria

The study will be open to all active duty personal who are:

- diagnosed with knee pain, categorized as anterior or retropatellar in one or both knees;

- self-reported difficulty performing at least two or more of the following activities associated with knee pain: prolonged sitting, stair climbing, running, jumping and repetitive movements such as kneeling or squatting or stooping;

- military service member at the time of diagnosis;

- age ≥18 and <45 years; and

- ability to provide freely given informed consent.

Exclusion Criteria

Those who might be at risk of adverse outcomes from the study interventions will be excluded. This includes individuals with

- Fracture or injury to external knee structures such that knee extension or flexion is impaired;

- A significant co-morbid medical condition (such as severe hypertension, neurological disorder or pacemaker/defibrillator) in which NMES strength training or unsupervised exercise is contraindicated and would pose a safety threat or impair ability to participate;

- Previous knee surgeries (i.e., tibiofemoral, patellofemoral) excluding knee arthroscopy;

- Knee instability or recurrent patella dislocation or subluxation;

- Inability or unwillingness to participate in a home exercise program or strengthening program;

- Inability to speak and/or read English;

- Reduced sensory perception in the lower extremities;

- Pregnancy;

- Vision impairment, where participant is classified as legally blind;

- Unwillingness to accept random assignment; or

- A score of 23 or greater on the Center for Epidemiological Studies-Depression scale (CES-D).

Note: For participants with bilateral knee pain (PFPS), the index knee will be the more severe knee as determined by diagnosis and the participants' report of pain and activity limitation.

Statistical Methods – See Statistical Analysis Plan.