Clinical Comparison of Patellofemoral Pain Syndrome Outcomes after Blood Flow Restriction Training

Clinical Trial Number: NCT05617911

Use date of study closeout: October 10, 2023

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

1. Methods

1.1 Study design

This study will be a multisite, randomized, sham-comparator controlled clinical trial conducted by Gaylord Specialty Healthcare Physical Therapy, (GSHPT) in Wallingford, Cheshire, Cromwell, Madison, CT, and the University Of Connecticut Health Center (UCHC) in Farmington, CT. All physical therapy related sessions will be conducted at the GSHPT locations listed above. Due to the nature of the intervention, participants and investigators will not be able to be masked to the intervention. Participants may not know they are in the intervention or sham group and therapists will not confirm or deny their placement. The assessor will not be able to be masked to group assignments, as the presence or absence of certain variables in the dataset, namely the use of BFR inflation, will immediately reveal group assignment.

Sample size:

An *a priori* power analysis for a two-tailed t-test was performed for sample size estimation. With an alpha = .05, power = 0.80, and effect size of 0.635, the projected sample size needed for complete data sets is approximately N = 80. Thus, our proposed sample size of N = 96 will be more than adequate for the main objective of this study, and should also allow for an expected attrition rate of 20%. Recruitment for this study will remain open until the target N of 80 complete datasets have been collected. This power analysis was performed using data from Dolak's[1] study on PFPS conducted in 2011. Sample size and protocol was also influenced by Brightwell's study on BFR after patellar instability[2].

Study Timeline:

Participants will be enrolled in the study for approximately 1 year. Starting with their evaluation and consent at the beginning of their therapy sessions, they will complete prescribed therapy and continue to complete PROs within 4-week, 9-week, 6-month and 12-month intervals. We anticipate the study will take approximately 3 years to complete.

Participants and Settings:

Participants will be males and females at least 15 years of age, recruited from the University of Connecticut Health Center (UCHC) and Gaylord Specialty Healthcare Physical Therapy, (GSHPT). Potential study participants will be identified upon evaluation by members of the UCHC and GSHPT clinical teams based on their presentation of PFPS. A clinical diagnosis indicated by a referring physician or the physical therapist conducting the initial evaluation is needed to participate in the study. Clinical history entails a review of previous medical records documenting knee pain, symptoms, treatments, and outcomes along with any current referral notes from outside clinicians and the participant's completed self-assessments which are done before the PT evaluation. According to the Journal of Orthopedic Sports Physical Therapy, PFPS is diagnosed by (1) the presence of retropatellar or peripatellar pain, (2) reproduction of retropatellar or peripatellar pain with squatting, stair climbing, prolonged sitting, or other functional activities loading the PFJ in a flexed position, and (3) exclusion of all other conditions that may cause anterior knee pain, including tibiofemoral pathologies. The physical exams GSHPT use includes meniscal tests, ligamentous stress tests and joint specific loading tests to rule out more specific injuries. The combination of findings from both the clinical history and physical exam and the diagnoses, allows the PT to exclude leads to the last catchall diagnosis, which is PFPS. There is not a clearly defined test or process to determine a PFPS diagnosis, so clinical judgment is relied upon for the ultimate diagnosis.

The clinical diagnosis is determined by an integration of both clinical history and physical exam findings, as well as by excluding other musculoskeletal and medical problems with thorough assessment of clinical history, risk factors, and physical examination. This is an exclusionary diagnosis that presents with generalized anterior knee pain surrounding the patella after excluding other sources of AKP such as patellar tendinopathy, trauma injury and arthritis.

To be eligible for study participation, subjects must meet the following Inclusion Criteria:

Diagnosis of patellofemoral pain syndrome (PFPS), which may be listed as non-specific anterior knee pain (NSAKP) of one or both knees, and plan to attend a participating GSHPT site.

Those who present one or more of the following Exclusion Criteria will not be eligible for study participation, including:

- Member of a defined vulnerable population, women who are or suspected to be pregnant, prisoners, children under 15, or other protected populations
- Body mass of the leg preventing the cuff from fitting properly
- Radiographic evidence of osteoarthritis (≥ Kellgren-Lawrence Grade 2)
- History of intra-articular injection into either knee within 3 –months
- Uncontrolled or untreated inflammatory disorder
- Acute inflammatory disorder
- Uncontrolled Diabetes and/or peripheral neuropathy, impaired circulation
- Uncontrolled cardiac conditions including uncontrolled hypertension
- Areas of thrombophlebitis, thrombosis
- Distal wounds or pain below the knee that is >4/10. This level is self-reported by the patient and is based on the Numeric Pain Rating Scale. Patients are asked to rate their pain level on a 0 to 10 scale with 0 being no pain at all and 10 being the worst pain imaginable. Typically, a pain level of 4 or greater is considered the clinical cutoff for continuation or inclusion in a treatment or activity.
- History of or current rhabdomyolysis
- Prolonged immobilization (>3 months)
- Sickle cell anemia
- Lymphadenectomy
- Varicose veins, or a history of personal or immediate family history (parental or sibling) of deep vein thrombosis
- Current infection at or below the level of cuff placement
- Malignancies in or below the area to be treated
- Other conditions/medications that would interfere with subject safety or data collection in the opinion of the PI
- Subjects with an increased risk of non-response as determined by the therapist
- Once entered in the study, a diagnosis change that affects participation. These diagnoses may be pregnancy, a new infection below the cuff level or one that could not be determined until the patient began and in some cases completed PT. Patients whose insurance will not cover imaging tests until they have completed a PT series are eligible since they are presenting with PFPS and

may be ins search of a diagnosis. They and their PT are progressing through the exploratory and exclusionary process and if warranted by the Exclusion Criteria will be removed from the study.

Equipment and Instruments:

Several pieces of equipment and outcome instruments will be utilized in this study. SmartCuffs (Smart Tools Plus, LLC, Cleveland, OH) Blood Flow Restriction Cuffs will be the primary piece of equipment used to complete the intervention portion of this study. The SmartCuff has a Personalized Pressure feature built into it. This feature allows for a personalized pressure calculation based on the patient's limb dimensions and blood flow. With the built-in pressure sensor and on-board computer, it will calculate and set the optimal pressure needed without the need for an external doppler probe or hand pump used by the PT. All study locations utilize this automated BFR cuff. Staff will be trained and/or retrained to ensure consistent practice across sites.

To obtain objective strength measures across the patient's treatment duration, isometric handheld dynamometry using a Mark-10 force gauge, model M3-500 (max capacity of 500 lb force/250 kg force/2500 newton force), will be completed by named investigators at initial evaluation, at 4-weeks, and at either the 9-week or discharge evaluation, whichever is first.

Several subjective outcome measures will be utilized throughout the study. Function specific subjective outcome measures include: Lower Extremity Functional Scale (LEFS), Knee Injury and Osteoarthritis Outcome Score for patellofemoral pain and osteoarthritis (KOOS-PF), the Tenger Activity Scale, and the Single Assessment Numerical Evaluation (SANE). Pain levels will also be assessed utilizing the Numerical Rating Scale (NRS) Pain Scale, 1-10. The LEFS is a validated 20-question PROM survey used for the measurement of lower extremity function based on the patients' initial function, ongoing progress, and long-term outcome. The KOOS-PF is an 11-question survey that is used to assess five outcomes; they include knee related quality of life, activities of daily living, sport and recreation function, activities, and pain and symptoms. The SANE is a single-item question used globally to assess function. The Numeric Rating Scale is one question pain intensity scale that assesses pain level on a 1-10 scale. The Fear Avoidance Beliefs Questionnaire (FABQ) is a 16 question likert scale questionnaire aimed at assessing how everyday activities assess the patient's current level of pain. The Tenger Activity Scale determines the level of activity prior and post injury. It will be collected at evaluation, 6 months and 12 months. The dynamometry, LEFS, SANE, NRS and KOOS-PF are documented during the initial evaluation, 4-week, and 9-week or at the end of PT. The PROs will be completed at evaluation, 4-week, 9-week or at the end of PT, as well as with a 6 month and 12 month follow-up. See attachment for chart.

Activity	Enrollment	Baseline	4-week	9-week or end of PT	6 months	12 months
Assessed for eligibility			X			
Demographics/baseline activity level			X			
Randomization			X			
Group allocation			X			
PT session			X			
Intervention Group only BFR w/PT	X		X	X	X	
Control Group sham BFR w/PT	X		X	X	X	
PROs	X	X	X	X	X	

Subject identification, recruitment, and pre-assessments:
Potential study participants will be identified via initial physical therapy evaluation as demonstrated clinical diagnosis. Clinical diagnosis is determined by an integration of both clinical history and physical exam findings, as well as by excluding other musculoskeletal and medical problems with thorough assessment of clinical history, risk factors, and physical examination. People may come to GSHPT with a diagnosis already in place, or they may be diagnosed by the Physical Therapist conducting the exam. Recruitment for the study will take place at four GSHPT locations: Cheshire, Cromwell, Madison, and Wallingford. Referrals for possible eligible participants for knee pain related physical therapy may be made by the usual outside referral sources. The study recruitment flyer will be shared with some of GSHPT's usual referral sources.
Once a diagnosis is reached, the patient will meet with a member of the study team. If the patient meets all inclusion and exclusion criteria, a study team member will begin the process to obtain informed consent. Consent will occur before any enrollment and treatment procedures are performed.

Subject assignment:
Consented subjects will be assigned to either the sham-comparator control group or BFR Intervention Group according to a pre-generated randomized assignment sheet. Each randomized assignment sheet will consist of equal control and equal BFR assignments whose order has been randomized using the random list generator at https://www.random.org/lists/. We will use blocked randomization to reduce the risk that patients will be assigned to the BFR treatment and sham control groups at unequal frequencies. These blocks will have a size of 6. Co-Investigators at each site will be given a unique list with a number of assignments that is in proportion to the number of subjects expected to be recruited at the site; additional assignment lists will be generated if needed. These co-Investigators will be responsible for communicating group assignments to study therapists delivering the intervention, and for ensuring that randomization and treatment order is maintained. It is expected that if the assignment scheme is not maintained for whatever reason, that they will report the incident to the PI and how it was/or still needs to be rectified. No matter group assignment, all consented subjects will be asked to conduct all assessments. Utilizing a proposed sample size of 96 participants, the study will continue until there are at least 40 participants who complete all study related activities in both the intervention and control groups.

Study protocol:
After being identified as a potential study participant and being consented, participants will be randomly assigned to the sham control or BFR group. All physical therapy sessions will consist of typical, standard

of care treatment. The treatment plan for people with PFPS who consent to participate will follow a defined schedule of exercises done in conjunction with BFR. This schedule is listed below as Exercise Protocol. The BFR training will be incorporated into the standard therapy sessions and will not elongate the treatment session, quantity of sessions or incur any additional cost. The sham control group will also follow the study Exercise Protocol in their physical therapy sessions. The sham control group will follow a typical standard of care physical therapy protocol based on their ability to complete sets with increased load and repetitions and pain tolerance and have a non-inflated BFR cuff placed in the same position as the intervention group. Similar to the intervention group, as participant's progress in therapy, the Physical Therapist will use their clinical decision making to advance the person through resistance and repetition increases.

A traditional physical therapy evaluation including isometric dynamometry and PROs including the Lower Extremity Functional Scale (LEFS), Knee Injury and Osteoarthritis Outcome Score for Patellofemoral Pain (KOOS-PF), Numeric Rating Scale (NRS), Fear Avoidance Beliefs Questionnaire (FABQ), and the Single Assessment Numerical Evaluation (SANE) will be used for data collection. Dynamometry will be tested at 90 degrees of knee flexion in a seated position with the dynamometer perpendicular to the distal tibia.

The dynamometry measurement is information is routinely collected upon admission to the GSHPT program for people presenting with knee pain. Once in position with an ankle cuff on, the participant will be instructed to perform one warm up test with about 50% effort. They will be cued to "kick slowly into the resistance, ramping up to a moderate effort". After a short rest, they will then be instructed to give 100% effort. Investigators will tell participants to "Kick again into the resistance, ramping up slowly over a few seconds until you are pushing as hard as you can, sustaining this for a few seconds". Participants will be encouraged to give full effort on this second attempt.
Participants will follow the exercise protocol as listed below:

Exercise Protocol
1. A 5-10 minute warm up on a bike or completion of the 6-Minute Walk Test will be utilized to start each session.
2. Establish a 10 repetition maximum (RM) for all exercises, pain dependent
3. 30% of established 1RM will be utilized for all exercises, each with 4 sets performed to failure (with pain </= 3 or 4/10)
4. One group will utilize BFR between 40-80% occlusion, and the sham group will use a non-inflated BFR cuff.
5. The exercise plan will be a combination of knee dominant, hip dominant, closed chain, and open chain exercises.
6. Different 'phases' of exercise programs performed to failure will be utilized depending on sensitivity levels of each patient. "Exercising to failure" is performing the exercise with the accompanying weights, bands, or body weight as appropriate to the specific exercise with as many repetitions as tolerable to the person with an acceptable pain level. It is determined by the participant, and while they may be encouraged by the therapist, they are not coerced to push beyond their comfort level.
a. Phase 1: (baseline pain > 3 or 4/10 OR weeks 1-4)
    i. Isometric wall squat @ 60 deg knee flexion (for time)
    ii. Romanian Deadlifts (DB or KB)
    iii. Low box step up
    iv. Knee extensions (90-45 deg flexion)

v. Standing Hip abduction

b. Phase 2: (Baseline pain <3 or 4/10 OR weeks 5-8)

i. Squats to a box (with external weight, height dependent on patient)

ii. Romanian Deadlifts (DB or KB or BB)

iii. High box step up

iv. Knee extensions (full ROM)

v. Standing Hip abduction

Individual exercises will progress based on the discretion of the treating physical therapist. A general guideline might include increasing the resistance when sets to failure are >15 repetitions without exceeding a 3 or 4/10 pain during or after each exercise.

1.2 Data collection and analysis

Along with their standard therapy session reassessments (including routine session notes and progress notes), participants will be asked to complete the PROs at 4-week, 9-week or at the end of PT sessions, 6-month and 12-month intervals. The PROs will be completed by paper and pen while at a therapy session. Baseline, 4-week, and 9-week or end of PT sessions assessments will be completed as part of the routine PT session evaluation process. If the participant is not coming in to Gaylord for appointments, the 6 and 12-month assessments will be completed by phone with the participant or paper copies will be mailed to their last known address. If necessary, an email will be sent to remind them of the study and scheduled assessments.

Information regarding the security of participant's data will be shared with them in the consent form as well as upon request. All information collected specifically for the study will be stored on password protected computers in locked offices. The paper copies of the assessment forms completed as part of routine PT sessions will be stored according to Gaylord procedures in the hard copy of the patient's medical record. Information from the forms will be pulled by study staff and shared across sites only after it is de-identified.

After data is collected and de-identified, it will be analyzed using GraphPad Prism version 9.3.1, or other appropriate statistical software as necessary. Adjustments for abnormal distribution and unequal variance will be applied as necessary. To compare pre- and post-intervention measurements over time on subjective and objective outcome measures, we will use a two-way repeated measures analysis of variance or independent samples t-test to determine the effect of treatment groups (BFR + standard of care therapy and sham + standard therapy). For relationships between variables, we will use correlation and regression analyses as necessary. For categorical data, we will use chi-square testing or Fischer's exact test as necessary. Exact analysis for each test will depend on variance and distribution/normality of data set. We will perform an interim analysis at 50 % participant recruitment in order to assess the effects of the BFR therapy and safety for the subjects, and potential for change in sample size. We will not preclude the possibility of conducting other post-hoc data analyses as appropriate and approved by the IRB.

References

1. Constantinou A, Mamais I, Papathanasiou G, Lamnisos D, Stasinopoulos D. Comparing hip and knee focused exercises versus hip and knee focused exercises with the use of blood flow restriction training in adults with patellofemoral pain: a randomized controlled trial [published online ahead of print, 2022 Jan 5]. *Eur J Phys Rehabil Med*. 2022;10.23736/S1973-9087.22.06691-6. doi:10.23736/S1973-9087.22.06691-6
2. Brightwell BD, Stone A, Li X, Hardy P, Thompson K, Noehren B, Jacobs C. Blood flow Restriction training After patellar INStability (BRAINS Trial). Trials. 2022 Jan 28;23(1):88. doi: 10.1186/s13063-022-06017-1. PMID: 35090543; PMCID: PMC8796555.