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STUDY TITLE: Use of blood flow restriction (BFR) therapy in peri-operative rehabilitation following anterior cruciate ligament tear

APPROVED
Sept. 10, 2019
INSTITUTIONAL REVIEW BOARD

1. STUDY AIM, BACKGROUND, AND DESIGN ABSTRACT

The purpose of this study is to examine the effect of utilizing blood flow restriction (BFR) therapy both before and after anterior cruciate ligament reconstruction (ACLR) following a tear. BFR has been proposed to work by restricting arterial inflow leading to an oxygen depleted environment and the ability to induce muscle adaption at lower maximum repetition via reactive hyperemia. [8] Muscle atrophy occurs following ACL tear and reconstruction. [5] Thus, physical therapy is used in the peri-operative period to regain strength with the ultimate goal of returning to activity.

The goal of this investigation is to determine if using BFR during perioperative therapy would lead to increased and expedited strength gains. Additionally we would like to determine if BFR helps patients to pass the standard rehabilitative functional tests and return to play sooner. We will also look at patient reported outcomes metrics and pain scores to determine if BFR has a significant impact on the patient experience surrounding ACL tear and reconstruction.

We hypothesize that the BFR group will have significantly greater strength gains at all time points. Previous studies have shown that BFR has potential in increasing muscle torque generation and cross sectional area in the first six months following ACLR.[5, 7] However there is a lack of evidence regarding the use of BFR preoperatively as well. Additionally, differences in outcomes based on ACL graft choice as well as functional return to play tests following use of BFR have not been determined. We believe that the use of BFR in the perioperative period surrounding and ACL tear and reconstruction has the potential to significantly decrease muscle atrophy and lead to earlier return to sport.

2. SUBJECT POPULATION AND ELIGIBILITY

Subject Population

- Subjects will be recruited from our ambulatory sports medicine clinics. We will include patients aged 18-60 who suffered an ACL tear and are undergoing ACL reconstruction.
- Subjects will be excluded if they are undergoing revision ACL reconstruction, history of DVT, neurovascular injury, unable to tolerate BFR treatment, unable to complete physical therapy, multiligamentous knee injury, peripheral vascular disease

Enrollment and/or Screening

- Subjects will be identified when they present to our ambulatory clinics with ACL tears. We will not access the medical record prior to presentation to our clinics. At presentation we will discuss the project with potential subjects and if they express interest we will then delve further into the chart to ensure they do not meet any exclusion criteria. Additionally we will discuss exclusion criteria with the patient during a detailed history. We will develop a series of questions to screen for exclusion criteria, particularly relating to history or family history of DVT.

3. STUDY PROCEDURES

- Patients will be randomized via computer to prospectively undergo ACL rehabilitation using BFR or conventional therapy by physical therapists with extensive experience in ACL rehabilitation who will undergo training on use of BFR. Training will consist of a volunteer session during which a physical therapist certified in BFR will educate physical therapists interested in undergoing the training.

There will be no incentive provided for participation by the therapists and they may opt out of using BFR at any point. The investigators will also attend this session to become better trained in the use of BFR. Both groups will undergo similar protocols with the only difference being the use of BFR cuff during rehabilitation. The protocol for using the BFR cuff will be similar to previous studies examining BFR.[2] More specifically the physical therapists will be provided with a tourniquet that includes a pressure monitor. The skin will be protected with a sleeve and the cuff will be placed in the thigh well proximal to the knee joint. We will begin by determining the patient's limb occlusion pressure, which is conducted automatically by the cuff via built in doppler. Once this is done the cuff will be inflated to 80% of the limb occlusion pressure, which is the currently accepted recommendation in the literature and sufficient to achieve the desired effect of blood flow restriction. Rehabilitation will consist of a structured home exercise program prior to surgery. Patients will be provided video instruction and training on how to conduct this. We will instruct patients on how to perform home BFR and test them in the office to ensure competence. We will also instruct the patient that they may only do exercises for a maximum of five minutes and allow a three minute reperfusion time following exercise, a rule that will be followed during outpatient PT as well. Additionally warning signs for cuff intolerance such as increased pain, swelling, numbness/tingling of the lower extremity, swelling of the lower extremity, calf pain, shortness of breath or chest pain will be communicated to the patient. The home program will also be done with and without the use of BFR and only the group randomized to BFR will use the cuff during the home program. Following surgery patients will immediately be started in physical therapy. Therapy will consist of a structured program progressing from range of motion, to strength training and then functional tests. Protocol as follows, both groups will use the same protocol with the only difference being use of BFR. Again the BFR group will have the cuff inflated per the protocol outlined above, this will be under the guidance of the physical therapists. Patients will be limited to 5 minutes of exercises with the cuff inflated followed by three minutes of reperfusion time. Overall, PT sessions will last around 30-45 minutes:

- Pre-op: Home exercise program consisting of straight leg raises, quad contractions, seated leg extension without resistance
- Weeks 0-4:
    - Knee ROM 0-90° at 10 days, full ROM (0-125) by 2-4 weeks. Will monitor knee ROM and add extra PT if unable to get full extension past week one
    - Strength: Sets of straight leg raises, calf raises, assisted squats, leg curls, core work
- Weeks 4-8: Will add in knee extension with low resistance, single leg balance exercises and full squats. Include stairmaster at week 4 and elliptical at week 6.
- Weeks 8-12: Begin rotational exercise such as lunges with rotation, steps and balance with rotational components.
- 3-6 months: Return to running, plyometrics and agility exercises in a progressive manner

Throughout this protocol patients will have a pre-operative visit, an early 2 week post operative visit to check range of motion and wound healing, a six week visit to monitor range of motion and a three month visit prior to clearance to being return to more aggressive activity. Strength and range of motion will be recorded at each of these visits in order to assess the primary endpoint. This will be conducte with a handheld device and will add less then five mintues to the clinic visit.

Outcomes:

- Primary Outcome:
  - Strength to be measured via dynamometer at the three month post-operative visit
- Secondary outcomes
  - Strength comparison at the six week visit
  - Range of motion via goniometer
  - Pain via VAS pain scale at each visit
  - Quadriceps muscle size based on circumferential leg measurements

Data analysis: The primary endpoint of this study was a maximum repetition total work deficit of 15% between the BFR and control group as measured by dynamometer. This was based on previous data showing that a strength deficit of 15% represents a clinically significant difference that is not likely attributable to limb dominance. Work deficit was calculated in each group by comparing the operative leg with the nonoperative leg to obtain a deficit percent. In recent publication[6] we found that the standard deviation for the isometric QF strength asymmetry index (equivalent to total strength deficit) ranges from 7% to 15%. Assuming a conservative standard deviation of 15%, with 80% power and type I error of 5%, we will need a sample size of 34 (17 patients per group) to detect a 15% total work deficit between the BFR and control groups.

All continuous data will be analyzed using independent 2-group t tests and reported as means ± standard deviations. Categorical data will be compared between the 2 groups using chi-square tests and reported as counts and percentages. A preliminary test to confirm the quality of variances will be conducted prior to utilizing the t test to confirm the appropriate statistical analysis. Nonparametric equivalents Wilcoxon rank-sum and Fisher exact tests will be used as needed for nonnormal distributions and low variable numbers, respectively. A multivariable regression analysis was performed to assess for potential confounding demographic variables.

Plan to recruit patients starting in May 2019. Will enroll patients and collect data from May-2019 to May 2020. Manuscript writing and submission to occur in June 2020.

4. ANTICIPATED RISKS

Patients may experience discomfort from the blood flow restriction (BFR) cuffs. Previous studies have shown that prolonged tourniquet use can lead to pain, nerve injury, and swelling. Recent advancements in tourniquets have resulted in complication rate of .04-.08% when used during orthopedic surgeries.[4] Recent studies specifically on use of tourniquets for BFR have found very low complication rate and we will be using the tourniquet for a very short duration of time. There is concern that BFR may increase the risk of DVT, however multiple studies have shown that BFR does not increase thrombin clot generation in in-vivo models.[1, 3] Regardless, in order to minimize risk we will exclude patients with a history or family history of DVT. Additionally, patient information will be kept de-identified on a password protected henry ford computer for the duration of the project. There is a minimal risk of privacy breach as only individuals who would regularly be involved in the peri-operative care of an ACL tear patient will be included in the study.

5. ANTICIPATED BENEFITS

- Potential benefits include faster return to play following ACLR, less pain following surgery, better ROM and a better overall satisfaction and result following ACL tear and reconstruction.

6. RENUMERATION/COMPENSATION

- No compensation offered

7. COSTS

- Additional costs will primarily be focused on obtaining the pressure cuffs. The payment for this will be provided by the investigators. Additionally, there will be some time cost to train the patient and physical therapists on use of the cuffs, however this will be minimal additional time and voluntary. There are no additional monetary costs.

8. ALTERNATIVES

Patients do not have to participate in this study and are able to undergo typical physical therapy as is the current standard.

9. CONSENT PROCESS AND DOCUMENTATION

Consent will be obtained from patients to participate in this investigation. We will obtain consent during a preoperative clinic visit. All research personnel listed in the IRB including the PI and associates will be responsible for informed consent. This will be done at the end of clinic visits to ensure there is ample time to answer questions. Additionally, contact information will be provided for questions throughout the entire process. Consent or lack thereof to participate will in no way effect the level of care provided for each patient. If at any point the patients no longer wish to participate they will be placed back into the usual post-operative care pathway. Minors will be consented along with their parents and either patient or parent may elect to participate or withdraw from the study. Patients will all be English speaking and have capacity to self consent. Documenting consent will be done during the clinic visit. Documentation will be stored in a locked room and kept in a folder with no visible identifying information.

Information will be kept in a locked area only accessible to study personnel. This will be kept in folders so there is no visible identifying information. The results of questionnaires and functional tests will be kept on a password protected HF computer and there will be no identifying information aside from MRN kept on these forms. All data will be destroyed following publication of this study or after six months of inactivity.

10. WITHDRAWAL OF SUBJECTS

- Subjects will be withdrawn from the study if they are unable to tolerate the BFR therapy. Additionally if they suffer from any complications of the therapy they will be withdrawn immediately. This will be facilitated by describing the reasons for withdrawal to the patient prior to initiating the study and ask patients and other providers to inform the investigators if there are any issues or concerns.
- Data collection on patients who were withdrawn will be terminated and data destroyed.
- Patients may withdraw from the study at any time for any reason without affecting the quality of their care

11. PRIVACY AND CONFIDENTIALITY

Data will be stored on a password protected HFH computer. Patient data will either be located in the chart

or kept in a locked spreadsheet that contains no patient identification aside from a unique patient ID associated with their MRN. This will only be accessible to the investigators. Data will be destroyed following publication or after six months of inactivity. We will also obtain HIPAA authorization in order to access the medical record.

12. DATA AND SAFETY MONITORING PLAN

We will be consistently checking in on patient safety as they undergo the usual post-operative ACL protocol. This will involve clinic visits in which we monitor the PT progress as well as the patient's adherence to the protocol. We will also be in weekly communication with therapists regarding patient progress and ability to complete protocol.

Unanticipated Problems and Adverse Events

We will report any problems or adverse events to the IRB via email

13. QUALIFICATIONS OF THE INVESTIGATOR(S)

Vasilios Moutzorous , MD Medical Education: Loyola University Medical School, Chicago, IL, Residency: Tufts University, Boston, MA, Orthopedic Surgery, Fellowship: Cleveland Clinic, Cleveland, OH, Sports. Additionally he has conducted and published multiple clinical trials and has extensive experience in the academic arena. The co-investigators are all medical school graduates and current orthopedic residents at HFH. Each has experience with conducting medical research and has multiple recent publications in medical literature.

14. REFERENCES

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