

AWARD NUMBER: W81XWH-20-1-0449

TITLE: Altering Post-Traumatic Osteoarthritis after Patellar Dislocation: Blood Flow Restriction Training, Aspiration, and Intraarticular Normal Saline (BRAINS Trial)

PRINCIPAL INVESTIGATOR: Cale Jacobs, PhD

CONTRACTING ORGANIZATION: University of Kentucky, Research Foundation,
Lexington, KY

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14. ABSTRACT Patellar dislocations are more common in military personnel and athletes than in the civilian population. In the short-term, muscular impairment after patellar dislocation impacts military readiness and in the long-term, patellar dislocation often leads to posttraumatic osteoarthritis (PTOA) within 5 to 15 years after injury. Physical therapy is the standard of care after patellar dislocation; however, despite the risks of PTOA and functional impairment after patellar dislocation, the conservative treatment of these injuries has remained largely unchanged over the past 20 years. There is no consensus on best practices and current treatment algorithms do not address both biologic and biomechanical mechanisms of PTOA. The purpose of this study is to determine if knee aspiration and saline injection or blood flow restriction training (BFRT), either individually or combined, will improve outcomes after patellar dislocation. The proposed study directly relates to the FY19 PRMRP Topic Area of Post-Traumatic Osteoarthritis (PTOA). The proposed multidisciplinary study addresses three Areas of Encouragement related to PTOA: 1) Studies to evaluate and develop best practices for multidisciplinary team approaches and treatment algorithms for post-traumatic osteoarthritis, 2) Intra-articular treatments that offer sustained (2 or more months) relief of symptoms and/or disease-modifying effects, and 3) Development of innovative rehabilitation approaches for preventing or mitigating PTOA. The results of this study will benefit military personnel and civilian patient populations to improve clinical outcomes after patellar dislocation, promoting a safe return to activity while also reducing degenerative changes to both the cartilage and muscle. The low cost and simplicity of the interventions will allow for immediate implementation in clinical practice in military and civilian settings.					
15. SUBJECT TERMS None listed.					
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1. Introduction

Patellar dislocations are more common in military personnel and athletes than in the civilian population. In the short-term, muscular impairment after patellar dislocation impacts military readiness and in the long-term, patellar dislocation often leads to posttraumatic osteoarthritis (PTOA) within 5 to 15 years after injury. Physical therapy is the standard of care after patellar dislocation; however, despite the risks of PTOA and functional impairment after patellar dislocation, the conservative treatment of these injuries has remained largely unchanged over the past 20 years. There is no consensus on best practices and current treatment algorithms do not address both biologic and biomechanical mechanisms of PTOA. The purpose of this study is to determine if knee aspiration and saline injection or blood flow restriction training (BFRT), either individually or combined, will improve outcomes after patellar dislocation. The proposed study directly relates to the FY19 PRMRP Topic Area of Post-Traumatic Osteoarthritis (PTOA). The proposed multidisciplinary study addresses three Areas of Encouragement related to PTOA: 1) Studies to evaluate and develop best practices for multidisciplinary team approaches and treatment algorithms for post-traumatic osteoarthritis, 2) Intra-articular treatments that offer sustained (2 or more months) relief of symptoms and/or disease-modifying effects, and 3) Development of innovative rehabilitation approaches for preventing or mitigating PTOA. The results of this study will benefit military personnel and civilian patient populations to improve clinical outcomes after patellar dislocation, promoting a safe return to activity while also reducing degenerative changes to both the cartilage and muscle. The low cost and simplicity of the interventions will allow for immediate implementation in clinical practice in military and civilian settings.

2. Keywords

Patella, dislocation, instability, rehabilitation, strength, effusion, cartilage, intra-articular injection

3. Accomplishments

What were the major goals of the project?

Major Task 1: Acquire protocol approvals (Completed 100% of specific objectives as reported in previous Quarterly Report) Major Task 2: Prepare for data collection (Completed 100% of specific objectives as reported in previous Quarterly Report) Major Task 3: Participant recruitment, evaluation (100% of recruitment preparation completed and screening began on 09/08/2020; 2/156 patient enrolled to date)
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What was accomplished under these goals?

Major Task 1: Acquire protocol approvals

Regulatory Approvals

- Local IRB Continuation Review approval at the University of Kentucky (01/11/2021, IRB# 56541)
- Submitted HRPO continuation review materials on 01/19/2021 (HRPO Log numbers E01432.1a (UK Site) and E01432.1b (CCF Site))
- Trial posted on clinicaltrials.gov (08/31/2020, NCT04554212)
- Received approval from UK Vice President of Research's Office to resume study activities involving human subjects as part of the University's phased resumption of research plan secondary to the COVID-19 pandemic (08/05/2020)

Major Task 2: Prepare for data collection

Develop REDCap database to record subject information and patient-reported outcomes, and test randomization module, data management, and quality control prior to enrolling patients

- Original Timeline (Months 1-3); Completed 09/08/2020

Finalize procedures for collection and processing synovial fluid, blood and urine specimens

- Original Timeline (Months 1-2); Completed 08/17/2020

Finalize procedures for biomechanical data collection

- Original Timeline (Months 1-2); Completed 09/17/2020

Finalize MRI collection and transfer process

- Original Timeline (Months 1-3); Completed 07/30/2020

Modify existing Physical Therapy recording software (MS Access)

- Original Timeline (Months 1-3); Completed 07/21/2020

Modify existing Manual of Operations with data collection methods and intervention specifics

- Original Timeline (Months 2-3); Completed 09/17/2020

Milestone Achieved: Manual of Operations created

- Original Timeline (Month 3); Completed 09/17/2020

Milestone Achieved: Research staff trained

- Original Timeline (Month 3); Completed 07/30/2020

Major Task 3: Participant recruitment, evaluation

Milestone Achieved: Patient enrollment initiated

- Original Timeline (Month 4) but were able to initiate screening in Month 3 on 09/08/2020
- First participant consented on 09/09/2020; however, the patient withdrew prior to undergoing any study activities. The participant is a minor who lives outside of Lexington, and her parents deemed that it would not be possible to attend the physical therapy sessions in Lexington.
- Second participant consented on 04/06/2021; however, the patient withdrew prior to undergoing any study activities after testing positive for COVID-19.

Continue subject recruitment (Target accrual rate: 1.2 participants/week)

- We have research personnel imbedded at the UK Sports Medicine Center who is screening patients from 7 different providers on a daily basis.
- We have continued screening but with COVID-19 related sports restrictions, the number of eligible patients is greatly reduced this year when compared to previous years. However, patient volumes have been gradually increasing clinically and we are actively working to improve enrollment by engaging additional clinicians and sites. Changes have been made to help improve enrollment which are described in more detail in the Changes/Problem section below.

Meetings with full research team (Quarterly)

- We did not have a large-group meeting this quarter. Instead, the PI met individually with Co-Investigators to discuss implementation of data collection and difficulties with enrollment. In addition, the PI meets weekly with clinic-based research coordinators to discuss enrollment and other day-to-day study administration. The Co-PI, Brian Noehren, PT, PhD also meets weekly with the physical therapy team.

Create DSMB report (Every 4 months)

- The initial DSMB report was completed, and was reviewed by the DSMB on 10/28/2020 and approved on 12/02/2020.
- The most recent DSMB report was reviewed and approved by the DSMB on 06/09/2021.

Major Task 4: Data analysis and dissemination of results

Process biomechanics assessments with existing Matlab and Labview batch programs (scheduled to begin in month 4)

- No data was analyzed since no data collection has been completed to date.

Analyze MRI scans (scheduled to begin in month 4)

- No data was analyzed since no data collection has been completed to date.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

The primary concern is the lack of enrollment. First, with sporting activities fully resuming, we are confident that our patient volume will return to pre-COVID levels in which we routinely saw between 7 and 9 eligible patients per month. Our rate over the past year has been < 1 patient per month. Second, we have learned more about local referral patterns and are working with Shriners Hospital for Children to increase the number of potentially eligible patients that are approached about the study. We have learned more about the local referral patterns and any patients under the age of 18 that suffer a patellar dislocation that are initially seen in the UK HealthCare Emergency Department are referred for additional evaluation at Shriners Hospital. Benjamin Wilson, MD was also added to the protocol as a sub-investigator, and Dr. Wilson is an orthopaedic surgeon at the University of Kentucky and routinely treats patients with patellar instability. Shriners is staffed by University of Kentucky surgeons thereby creating a viable option to improve recruitment. Dr. Wilson and other University of Kentucky surgeons routinely treat patients with patellar instability at this facility. The surgeon will discuss the study with

potential participants and information given on how to proceed should they be interested in participating. Enrollment would occur in-person at the UK Orthopedics & Sports Medicine Center. We have created an IRB-approved recruitment flyer and have received administrative approval from Shriners to begin this process starting in August, 2021. Additionally, to help achieve the study goals, we will continue our weekly local team meetings as well as our quarterly meetings involving all study investigators at both sites. Once patients have been enrolled and data collected, the research team at the Cleveland Clinic will begin analyzing the MRI images.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. Changes/Problems

Nothing to Report

6. Products

Altering Posttraumatic Osteoarthritis after Patellar Dislocation: Blood flow Restriction training, Aspiration, and Intra-articular Normal Saline (BRAINS Trial). Benjamin D. Brightwell, DPT; Austin Stone, MD, PhD; Xiaojuan Li, PhD; Peter Hardy, PhD; Katherine Thompson, PhD; Brian Noehren, PT, PhD; Cale Jacobs, PhD. Trials. In Review (Submitted March 26, 2021).

**The draft manuscript has been included in the Appendix*

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Cale Jacobs, PhD
Project Role:	PI (University of Kentucky)
Researcher Identifier (e.g. ORCID ID):	0000-0002-9300-5550
Nearest person month worked:	2
Contribution to Project:	Dr. Jacobs has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures.

Name: Brian Noehren, PT, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 2
Contribution to Project: Dr. Noehren has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures.

Name: Austin Stone, MD, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0002-9406-7884
Nearest person month worked: 1
Contribution to Project: Dr. Stone is the medical director for the project and has been involved with finalizing the inclusion/exclusion criteria and screening and enrollment procedures.

Name: Katherine Thompson, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Dr. Thompson is the team's biostatistician and has been involved with the study design and implementing the randomization procedures. She will be involved throughout the project and will be responsible for all analyses performed at the conclusion of the trial.

Name: Peter Hardy, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0003-0956-0138
Nearest person month worked: 1
Contribution to Project: Dr. Hardy has worked on all aspects of MRI image collection and transfer, and will be involved with the analysis and interpretation of imaging results.

Name: Xiaojuan Li, PhD
Project Role: Site PI (Cleveland Clinic)
Researcher Identifier (e.g. ORCID ID): 0000-0002-0567-9935
Nearest person month worked: 1
Contribution to Project: Dr. Li has worked on all aspects of MRI image collection and transfer, and will be involved with the analysis and interpretation of imaging results.

Name: Benjamin Brightwell, PT, DPT, OCS, CSCS
Project Role: Graduate Assistant, Physical Therapist
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Mr. Brightwell has been involved finalizing the physical therapy program and exercise recording software in MS Access, and in preparation of the protocol manuscript for submission to BMC Trials. He will be directly involved with the day-to-day administration of the physical therapy program.

Name: Tara Spach
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Ms. Spach has participated in staff training and finalizing data collection and enrollment procedures. She will be actively involved with coordinator research testing and physical therapy sessions in the Biotion Lab.

Name:	Kelsey Reeves
Project Role:	Biomechanist
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1
Contribution to Project:	Ms. Reeves has participated in staff training and is responsible for biomechanical and strength testing being done as part of the trial.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Cale Jacobs, PhD

Active support that has been initiated since the last report (1)

Title: MONTelukast as a Potential CHondroprotective Treatment Following Anterior Cruciate Ligament Reconstruction (MOCHA Trial)

Role: PI

Supporting Agency: Arthritis Foundation

Performance Period: 11/01/2020 - 10/31/2022

Previous support that has been completed since the last report (3)

Title: Comparison of Tourniquet-Less TKA with the Aquamantys Bipolar Sealer and the Standard of Care in the Setting of Outpatient TKA

Role: Co-Investigator

Supporting Agency: Medtronic, Inc.

Performance Period: 10/30/2018 – 10/23/2020

Title: A Prospective, Single-Center, Randomized, Triple-Blinded, Placebo-Controlled study of IL-1RA Treatment in Patients with Acute ACL Tear and Painful Effusions

Role: PI

Supporting Agency: Arthritis Foundation

Performance Period: 01/2018 – 10/2020

Title: Cartilage breakdown and Arthrofibrosis after multiple ligament KneE injury (CAKE Trial)

Role: PI

Supporting Agency: University of Kentucky

Performance Period: 07/2019 – 06/2021

Brian Noehren, PT, PhD

Active support that has been initiated since the last report (3)

Title: Diversity Supplement: Mechanistic assessment of blood flow restricted training for an ACL injury

Role: PI/Mentor

Supporting Agency: NIAMS

Performance Period: 07/22/2020 - 06/30/2022

Title: Validation of Small Molecule Inhibitor to Improve Outcomes in Obesity, Insulin Resistance and Osteoarthritis (PILOT)

Role: Co-Investigator
Supporting Agency: NIGMS
Performance Period: 01/21/2021 - 07/31/2021

Title: Accelerating Recovery Following a Lower-Extremity Fracture Through Speed HIIT
Role: PI
Supporting Agency: Department of Defense
Performance Period: 08/01/2021 - 07/31/2024

Previous support that has been completed since the last report (2)

Title: Effect of Blood Flow Restriction Training on Functional and Self-Reported Outcomes in Runners with Patellofemoral Pain
Role: Co-Investigator
Supporting Agency: American College of Sports Medicine Foundation
Performance Period: 07/01/2020 - 06/30/2021

Title: Anterior Cruciate Ligament Injury Stimulates Cytokine Activation and Morphological Maladaptions in Patellar Tendon
Role: Co-Investigator
Supporting Agency: American College of Sports Medicine Foundation
Performance Period: 07/01/2020 - 06/30/2021

Austin Stone, MD, PhD

Active support that has been initiated since the last report (3)

Title: A Prospective, Multi-Center Study Evaluating ProChondrix CR for the Repair of Focal Articular Cartilage Defects in the Knee
Role: PI
Supporting Agency: AlloSource
Performance Period: 07/01/2020 - 05/10/2022

Title: ProChondrix® CR Articular Cartilage Restoration Evaluation (PACE) Registry
Role: PI
Supporting Agency: AlloSource
Performance Period: 07/01/2020 - 05/10/2022

Title: MOnTelukast as a Potential CHondroprotective Treatment Following Anterior Cruciate Ligament Reconstruction (MOCHA Trial)
Role: Co-Investigator
Supporting Agency: Arthritis Foundation
Performance Period: 11/01/2020 - 10/31/2022

Previous support that has been completed since the last report (2)

Title: A Prospective, Single-Center, Randomized, Triple-Blinded, Placebo-Controlled study of IL-1RA Treatment in Patients with Acute ACL Tear and Painful Effusions
Role: Co-Investigator
Supporting Agency: Arthritis Foundation
Performance Period: 01/2018 – 10/2020

Title: Cartilage breakdown and Arthrofibrosis after multiple ligament KneE injury (CAKE Trial)
Role: Co-Investigator
Supporting Agency: University of Kentucky
Performance Period: 07/2019 – 06/2021

Katherine Thompson, PhD

Active support that has been initiated since the last report (4)

Title: The SROCS Summer Research Conference in Statistics and Biostatistics

Role: PI

Supporting Agency: National Science Foundation

Performance Period: 07/01/2021 – 06/30/2022

Title: Understanding the Role of Immune Complexes Between Apolipoprotein A-I and IgG in Atherosclerotic Cardiovascular Disease

Role: Co-Investigator

Supporting Agency: National Institute on Aging

Performance Period: 07/01/2020 – 06/30/2024

Title: The Biological Mechanisms of Metformin Effects on Aging-Associated Inflammation

Role: Co-Investigator

Supporting Agency: National Institute on Aging

Performance Period: 09/15/2020 – 08/31/2021

Title: Optimizing Clinical Outcomes for Patients with Chronic Ankle Instability Using Foot Intensive Rehabilitation (FIRE)

Role: Co-Investigator

Supporting Agency: Army Medical Research and Materiel Command

Performance Period: 09/15/2020 – 09/28/2021

Title: Length-Dependent Activation in Human Myocardium

Role: Co-Investigator

Supporting Agency: National Heart Lung and Blood Institute

Performance Period: 09/15/2020 – 07/31/2024

Previous support that has been completed since the last report (1)

Title: Research, Data Analytics, & Measurement of Program Outcomes: 1115 Waiver

Role: Co-Investigator

Supporting Agency: Commonwealth of Kentucky, Cabinet for Health and Family Services

Performance Period: 07/01/2018-06/30/2020

Peter Hardy, PhD

Active support that has been initiated since the last report

Title: MOnTelukast as a Potential CHondroprotective Treatment Following Anterior Cruciate Ligament Reconstruction (MOCHA Trial)

Role: Co-Investigator

Supporting Agency: Arthritis Foundation

Performance Period: 11/01/2020 - 10/31/2022

Title: Multi-Vendor Multi-Site Novel Accelerated MRI Relaxometry

Role: Co-Investigator

Supporting Agency: Case Western Reserve

Performance Period: 05/01/2021 - 08/01/2021

Previous support that has been completed since the last report

Title: Novel pRNA Nanoparticle Delivery as Directed Therapy for Colorectal Cancer Metastasis

Role: Other Significant Contributor

Supporting Agency: National Institute of Health National Cancer Institute
Performance Period: 9/25/15 to 08/31/20

Xiaojuan Li, PhD (Cleveland Clinic)

Active support that has been initiated since the last report

Title: Multi-Vendor Multi-Site Novel Accelerated MRI Relaxometry

Role: PI

Supporting Agency: NIAMS

Performance Period: 05/01/2020 - 04/30/2025

Title: Enhanced MR for morphological characterization of ligaments, tendons and bone

Role: Co-PI

Supporting Agency: NIBIB

Performance Period: 08/05/2020 - 07/31/2025

Title: Osteoarthritis Virtual Center of Excellence

Role: PI

Supporting Agency: Arthritis Foundation

Performance Period: 08/01/2020 - 07/31/2023

Title: Injection of triamcinolone after arthroscopic partial meniscectomy

Role: Co-PI

Supporting Agency: Arthritis Foundation

Performance Period: 09/01/2020 - 08/31/2023

Title: MOnTelukast as a Potential CHondroprotective Treatment Following Anterior Cruciate Ligament Reconstruction (MOCHA Trial)

Role: Co-Investigator

Supporting Agency: Arthritis Foundation

Performance Period: 11/01/2020 - 10/31/2022

Previous support that has been completed since the last report

Nothing to Report

What other organizations are involved as partners?

Organization Name: Cleveland Clinic Foundation

Location of Organization: 9500 Euclid Ave, ND20
Cleveland, OH 44195

Partner's contribution to the project:

Collaboration: Xiaojuan Li, PhD is the Director of the Program in Advanced Musculoskeletal Imaging (PAMI) at the Cleveland Clinic. She will be directly involved with the analysis of the MRI images that are collected as a part of this trial. Her research program aims at developing novel quantitative imaging techniques to improve early diagnosis and prognosis for musculoskeletal diseases, and translating these advanced techniques to clinical practice to ultimately improve patient care. She has served as the PI of basic research and clinical research studies sponsored by NIH (K25, R21, R01, U01), private foundations, industry companies and universities, and has served as the imaging core director/chair for multicenter studies. Currently, she served as the Co-Chair of the quantitative imaging alliance (QIBA) subcommittee for cartilage compositional MRI biomarkers, sponsored by Radiologic Society of North America (RSNA), and serves on the Executive Committee of the Arthritis Foundation OA Center of Excellence Initiative. In August 2017, she moved from UCSF to Cleveland Clinic to expand her research program. She has served as the Founding Director of the Program of Advanced MSK Imaging

(PAMI), CCF. PAMI is a multi-institutional joint program between Lerner Research Institute, Imaging Institute, and Orthopaedics and Rheumatology Institute at Cleveland Clinic. Currently PAMI has more than 40 members and holds a monthly meeting for discussing ongoing collaborative research and planning strategic program development with new collaborations. With her expertise in this topic area, she is an invaluable member of the research team.

8. Special Reporting Requirements

Nothing to Report

9. Appendices

The following text beginning on the following page is the submitted draft of the protocol paper that is currently in review with *Trials*.

Altering Posttraumatic Osteoarthritis after Patellar Dislocation: Blood flow Restriction training,
Aspiration, and Intra-articular Normal Saline (BRAINS Trial)

Authors: Benjamin D. Brightwell, DPT¹, Austin Stone, MD, PhD¹, Xiaojuan Li, PhD², Peter Hardy, PhD¹,
Katherine Thompson, PhD¹, Brian Noehren, PT, PhD^{1*}, Cale Jacobs, PhD^{1*}

* Indicates co-senior authors

University of Kentucky¹

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Abstract

Background: Patellar dislocations are a common and understudied condition that disproportionately affects athletes and military personnel. The rate of post traumatic osteoarthritis that develops following a patellar dislocation can be up to 50% of individuals 5-15 years after injury. Conservative treatment is the standard of care following acute traumatic patellar dislocation however, there are no evidence-informed rehabilitation guidelines in the scientific literature. The purpose of this study is to assess the effectiveness of combined early aspiration/saline injection and blood-flow restriction training (BFRT) after acute patellar dislocation. Our hypotheses are that this multimodal strategy will improve patient-reported outcomes and accelerate restoration of symmetric strength and knee biomechanics necessary to safely return to activity.

Methods/Design: This is a randomized, double blinded, placebo-controlled clinical trial that aims to recruit 156 patients with acute patellar dislocations randomly allocated into four groups: 1) knee aspiration/saline injection + sham BFRT, 2) sham knee injection + BFRT, 3) knee aspiration/saline injection + BFRT, 4) sham knee injection + sham BFRT. All groups will receive current standard of care physical therapy 3 times per week for nine weeks. Physical therapy sessions will consist of typical standard of care treatment followed by BFRT or sham BFRT. Primary outcomes include the Norwich Patellar Instability Scale, quadriceps strength, and imaging and biochemical biomarkers of cartilage degradation.

Discussion: The current standard of care for non-operative treatment of acute patellar dislocations is highly variable does not adequately address the biological or biomechanical mechanisms necessary to restore lower extremity function and protect the long-term health of articular cartilage following injury. This proposed novel intervention strategy combines 2 easily implementable therapies to evaluate if the combination significantly improves patient reported outcomes, function, and joint health over the first year of recovery.

TRIAL REGISTRATION: BLOOD FLOW RESTRICTION TRAINING, ASPIRATION, AND INTRAARTICULAR NORMAL SALINE (BRAINS), NCT04554212. REGISTERED 18 SEPTEMBER 2020, [HTTPS://CLINICALTRIALS.GOV/CT2/SHOW/NCT04554212](https://clinicaltrials.gov/ct2/show/NCT04554212)

Keywords: Patellar Dislocation, Blood-Flow Restriction Training, Aspiration, Rehabilitation

Background

Patellar dislocations are a common and understudied condition that disproportionately affects athletes and military personnel [1]. The rate of having a patellar dislocation is greater than having an anterior cruciate ligament (ACL) tear in this population [1]. A significant long-term concern is the rate of post traumatic osteoarthritis that develops following a patellar dislocation which can be up to 50% of individuals within 5-15 years after injury [2]. Nonoperative treatment is currently the standard of care following most first-time dislocations; however, 31% of patellar instability patients treated conservatively suffer a re-dislocation [3]. A single patellar dislocation increases the lifetime risk of post-traumatic osteoarthritis (PTOA) and recurrent dislocations markedly increases this risk [2, 4]. Therefore, there is an urgent need to minimize the incidents of recurrent patellar dislocations and PTOA sequela which safely allows an earlier return to sport or work while also limiting long-term functional impairments and reduced quality of life.

While nonoperative treatment is most commonly employed following acute traumatic patellar dislocation, specific evidence-informed rehabilitation guidelines are sparse [3]. The lack of consistency is due, in large part, to not considering the varied and complex needs of treatment. Multidisciplinary nonoperative treatment protocols are needed to address both biologic and biomechanical mechanisms that affect short and long-term outcomes after patellar dislocation (Figure 1). To accomplish this goal, successful treatments will need to reduce the inflammatory burden, lessen cartilage degradation, and limit muscle impairment in order to improve patient outcomes and safely allow an earlier return to active duty and sport.

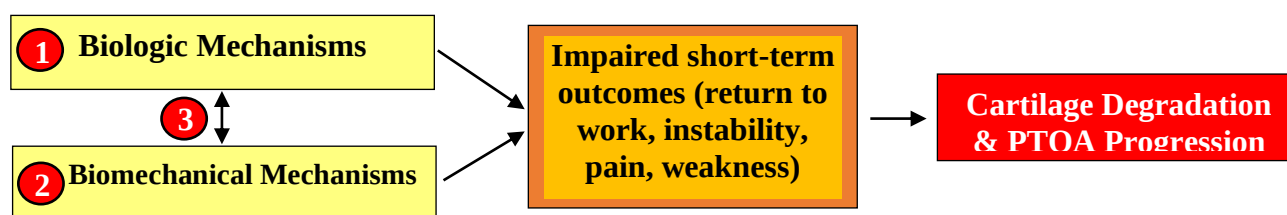


Figure 1. Theoretical framework depicting the individual and combined roles of biologic and biomechanical mechanisms on outcomes after patellar dislocation.

The proinflammatory cascade initiated after a patellar dislocation is not clear, but the catabolic response likely parallels that seen after an ACL injury. For example, the process of cartilage degradation begins immediately after acute knee injury with significant increases in synovial biomarkers of collagen breakdown after ACL injury [5, 6]. CTXII (a synovial biomarker of type II collagen breakdown) significantly increased during the first 4 to 5 weeks after an ACL injury [5, 6]. Much like CTXII, synovial fluid concentrations of proinflammatory cytokine interleukin-1 α (IL-1 α) and degradative enzyme matrix metalloproteinase-3 (MMP-3) significantly increased over the first 5 weeks after injury [5]. Cytokines, monocytes, and macrophages act as mediators in the cycle of cartilage degradation after acute knee injury and in knee osteoarthritis. As a result of cartilage breakdown proinflammatory cytokines including IL-1 β activate synovial macrophages. Macrophages then produce additional proinflammatory cytokines resulting in chondrocyte activation and production of MMPs thereby perpetuating the cyclical process of cartilage degradation [7]. There is emerging evidence to support early aspiration and saline injection to decrease the pro-inflammatory environment associated with hemarthrosis thereby reducing pain, cartilage degradation, and negative neuromuscular feedback associated with a joint effusion [8]. In the current study, knee aspiration and saline injection will be used to address these biologic mechanisms of PTOA progression.

Blood flow restriction training (BFRT) involves the use of an inflatable cuff applied to the thigh to slow arterial blood flow and eliminate venous return as subjects exercise with a relatively low resistance. It is thought that the increased metabolic stress and mechanical tension during BFRT act to stimulate various metabolic pathways leading to muscle hypertrophy [9-11]. There is evidence supporting the premise that BFRT will result in improved quadriceps and hip strength without the need for high intensity resistance exercise [12-14]. Due to the nature of acute patellar dislocations, patients may not tolerate high intensity quadriceps exercises early in the rehabilitation process thus delaying the recovery of strength. BFRT may allow them to receive the same training benefits as if they were training under high loads. Achieving greater muscle strength earlier after injury may result in improved lower extremity biomechanics, improved functional capacity, and an accelerated recovery.

The purpose of this double blind randomized clinical trial is to assess whether the combination of aspiration/saline injection and BFRT will improve patient-reported outcomes and accelerate return to work or sport through earlier restoration of symmetric strength and knee biomechanics, and reduce the early inflammatory response and cartilage degradation following patellar dislocation.

Methods/Design

Aims

The overarching rationale is that the novel combination of aspiration, saline injection, and BFRT will expedite the return to work or sports, minimize muscle impairment, and ultimately slow cartilage degradation over the first year following patellar dislocation. This strategy will improve patient-reported outcomes and accelerate restoration of symmetric strength and knee biomechanics necessary to safely return to activity. We will test the following specific aims:

AIM 1: Determine if early knee aspiration and/or BFRT improves patient-reported outcomes and lessens the time to return to work or sport following patellar dislocation.

Hypothesis: Combining early knee aspiration with BFRT will result in significantly improved responses on the patient-reported Norwich Patella Instability, visual analog scale (VAS) for Pain, Cincinnati Occupational Rating Scale, Tegner activity scores and an earlier return to work and/or sport.

AIM 2: Assess whether early knee aspiration and/or BFRT results in improved quadriceps strength and knee biomechanics following patellar dislocation.

Hypothesis: The combination of early knee aspiration and BFRT will result in improved quadriceps strength and knee biomechanics (knee moments and excursions).

AIM 3: Compare progressive changes in cartilage degradation and inflammatory profiles between groups treated with early knee aspiration and saline injection after patellar dislocation.

Hypothesis: Early knee aspiration and saline injection will reduce degradative changes on Magnetic Resonance Imaging (MRI) as well as serum and urinary biomarkers of inflammation and cartilage degradation.

Participants

Participants will be males and females recruited from the University of Kentucky Sports Medicine Clinic. A sample of 156 patients with patellar dislocations will be recruited. Before enrollment, each subject will provide written informed consent. An American Board of Family Medicine-certified physician with a Certificate of Added Qualifications in Sports Medicine or board-certified orthopaedic surgeon will make the diagnosis of patellar dislocation utilizing the following criteria: patients' report of at least one episode of patellar instability within the past 3 months, a positive patellar apprehension test during clinical examination, and no evidence on MRI or x-ray of loose body formation or osteochondral defects, avulsion, or osteochondral defect that would require the need for surgical intervention.

Table 1.

Inclusion and Exclusion Criteria for the BRAINS Clinical Trial for Patients with Patellar Dislocation

Inclusion Criteria
Diagnosis of traumatic patellar dislocation (either primary or recurrent) determined by an American Board of Family Medicine-certified physician with a Certificate of Added Qualifications in Sports Medicine utilizing clinical examination, radiographic imaging, and patients' reports of instability
Age 14 to 40 years
Skeletally mature with closed growth plates visualized by radiograph
A score of 80 or more on the Sports Activity Scale, which corresponds to participating in "running, twisting, turning (tennis, racquetball, handball, ice hockey, field hockey, skiing, wrestling)" at least 1-3 times per week
Desire to resume pre-injury activity level
Exclusion Criteria
Patellar subluxation but not dislocation
Concomitant osteochondral lesion requiring surgical fixation
Radiographic evidence of osteoarthritis ($\geq$ Kellgren-Lawrence Grade 2)

Previous ipsilateral or contralateral knee surgery
Most recent instability event more than 3 months before enrollment
History of intra-articular injection into either knee within 3 months
History of any inflammatory disorder
Body Mass Index > 35 kg/m ²
Diabetes or uncontrolled hypertension
Varicose veins or a history of personal or immediate family history (parental or sibling) of deep vein thrombosis

Design

This is a randomized, double blinded, placebo-controlled clinical trial that begins in the winter of 2020 and will continue for 4 years. This study will take place at the University of Kentucky, and has been approved by the University of Kentucky IRB (IRB #56541, ClinicalTrials.gov Identifier: NCT04554212).

Randomization, Group Allocation, and Blinding

All assessments will be done by a separate individual to the person allocating and either performing the study injection or applying the BFRT unit to ensure blinding. The study statistician will generate a randomization plan using SAS or R to assign subjects to groups. Randomization will occur by sex and be in sets of 4 subjects to ensure adequate distribution of all groups across the collection period. Patients will be randomized into one of the four following treatment groups:

- 1) acute knee aspiration/saline injection with standard of care physical therapy + sham BFRT
- 2) sham knee injection with standard of care physical therapy + BFRT
- 3) knee aspiration/saline injection with standard of care physical therapy + BFRT
- 4) sham knee injection with standard of care physical therapy + sham BFRT

Interventions

All patients, regardless of group allocation, will receive a subcutaneous lidocaine injection. For those randomized to undergo joint aspiration, joint aspiration will be performed aseptically via a superolateral suprapatellar approach. The aspiration syringe will be removed from the needle and a syringe containing 5 mL of normal saline will be attached, followed by injection [5, 6, 15].

All groups will receive current standard of care physical therapy. Physical therapy sessions will consist of typical standard of care treatment followed by BFRT or sham BFRT. The standard of care portion of the session will consist of brief subjective and objective screening followed by a structured treatment paradigm consisting of pain modulation, neuromuscular re-education, dynamic warm-up, range of motion and mobility, progressive strengthening and power training with emphasis on the lower extremities and trunk musculature. The standard physical therapy portion of the treatment session will last approximately 40 minutes. Interventions for pain modulation, range of motion, and neuromuscular re-education, balance, and gait training will be utilized as needed to address individual subjects' specific needs at the time of screening based on the severity of the injury and with the goal of adequately preparing them to return to their sport of choice.

Blood Flow Restriction Training

Two brands of blood flow restriction units will be used (brand names not included in this text to avoid the potential for subjects to become unblinded). Subjects will be split into groups as previously described where brand 1 will be used as sham BFRT and the intervention group will use brand 2. All quadriceps focused exercises will be performed with the bands inflated. As directed by the manufacturer's instructions, the bands will be placed on the proximal thigh as close to the femoroacetabular joint as possible (Figure 2). Limb arterial occlusion pressure will be constantly monitored and adjusted by the unit to maintain the desired occlusion pressure throughout the duration of exercise. Consistent with our current trial assessing the efficacy of BFRT for ACL reconstruction patients (NCT03364647), participants in all groups will perform the same exercises with an emphasis on



Figure 2: The BFRT band applied to the upper thigh of the subject's leg, pressure is regulated by the controller unit during training.

quadriceps and hip strengthening, and for those randomized to the active BFRT groups, each BFRT session will last approximately 20 minutes [16]. All subjects will attend 3 visits per week for 8 weeks divided in to 4 phases.

The active BFRT groups will have the arterial blood flow occlusion pressure set per manufacturer instructions to achieve the desired limb occlusion pressure (LOP), whereas the sham BFRT group will have restriction pressure set at a sub-clinical level of occlusion. Occlusion personalized tourniquet pressure (PTP) will be reassessed each visit by rechecking the LOP. Each subject will perform a block of 4-5 quadriceps and hip-focused exercises each lasting approximately 5 minutes for a total of 20 minutes (Exercises: seated single leg press, seated single leg knee extension, single leg forward step ups progressed to forward step downs when tolerated, and resisted double leg squats). Exercise intensity will be adjusted between groups to accommodate achievement of volitional fatigue and an acceptable sensation of discomfort during exercise. Cuffs will be deflated for a minimum of 1 minute between exercises. The quadriceps and hip strengthening exercises with the cuff donned will be performed at the end of the rehabilitation session with the intention of reducing the impact of fatiguing the muscles for the standard physical therapy portion of the treatment session.

For all subjects, rating of perceived discomfort and rating of perceived effort will be recorded from separate 11-point Likert-type scale (0 no discomfort or effort – 10 maximal discomfort or effort) for each BFRT exercise. Emphasis will be placed on distinguishing between effort (the amount of physical energy being given to the exercise) and discomfort (the physiological and unpleasant sensations associated with the exercise), with the goal of maximizing effort. All exercises should be challenging and/or hard to perform; however, subjects need to maintain proper form, as determined by the treating physical therapist, to ensure appropriate quadriceps engagement.

Criteria for progression of resistance or exercises include 1) No excessively aberrant movement causing pain due to fatigue of desired muscle group(s), 2) No excessive form deviation where the desired muscle group is no longer the primary mover completing the desired task, 3) No concordant pain > 4/10, 4) Ability to complete

delineated sets and repetitions without pausing within a set, and 5) Able to complete 2 or more repetitions than delineated during the last set of the exercise.

Treatment Adherence

Treatment adherence is the extent to which a therapist uses interventions prescribed by a protocol. To maximize adherence and treatment fidelity, electronic logs of all the exercises per session will be kept on a custom Microsoft Access database. Adherence to the treatment protocol will be audited by an external physical therapist regularly throughout the duration of the study. We will monitor session attendance using a diary log with participant ID numbers and session dates to track percentage of attendance and to account for absenteeism and reasons for missed sessions. We will make every effort to deliver the full treatment, but we expect some variation in treatment delivery dose as well as treatment drop-out. Reasons for attrition will be assessed with an open-ended question for enrolled participants who withdraw.

Outcome Measures

Primary outcomes include the Norwich Patellar Instability Scale, isometric and isokinetic quadriceps strength, MRI T1 ρ and T2 relaxation times, and biochemical biomarkers which will include urinary C-terminal cross-linked telopeptide type II collagen (CTXII) and a neoepitope of type I and type II collagen cleavage (C1,2C). Secondary outcomes include the VAS for pain, Cincinnati Occupational Rating Scale, Tegner Activity Scale and the time to returning to work and/or sporting activities, hip muscle strength (hip abduction, hip external rotation), and knee biomechanics (knee extensor moment, knee flexion excursion, knee adduction moment, knee adduction excursion) during walking, running, and anterior step-downs.

Table 2.

Flowchart of Study Activities						
Activity	Enrollment	1 week	4 weeks	9 weeks	6 months	12 months
Assessed for eligibility	X					
Demographics and Activity Level	X					
Randomized	X					
Sham vs. Study Injection	X					
Physical Therapy Sessions	X					
Patient-Reported Outcomes	X		X	X	X	X

Strength Testing		X	X	X	X	X
Biomechanical Assessment		X		X	X	X
MRI		X				X
Biochemical Biomarkers	X		X	X	X	X

Statistical Methods

The primary outcome variable for Aim 1 is the Norwich Patellar Instability Scale. Utilizing the standard deviation of 18.6 points from our pilot results, a sample size of 34 subjects per group will be adequately powered (80%) to detect a moderate effect size between groups difference (13 points difference, effect size = 0.7). To protect against up to 15% of subjects being lost to follow-up, an additional 5 subjects will be enrolled per group (39 subjects per group; 156 total). Based on our previous pilot work, a sample size of 34 patients per group will also be more than 80% powered to detect group differences in the primary outcome variables for both Aim 2 (quadriceps strength) and Aim 3 (T1ρ relaxation time).

Since all endpoints are quantitative and longitudinal data is collected, repeated measures analysis of covariance (ANCOVAs) will be used to assess differences in scales across the four treatment groups (combinations of two factors: acute knee aspiration/saline injection vs. sham knee injection, and BFRT vs. sham BFRT). The repeated measures ANCOVAs will adjust for demographic covariates (e.g., age, sex, and race) as well as look for differences across any other potential confounders (such as first-time vs. repeated dislocations). Assumptions such as normality and constant variance will be assessed, and remedial measures will be employed as needed. In addition, interaction effects and/or variable transformations will be explored appropriately. In the case that endpoints are related, multivariate analysis of covariance (MANCOVAs) may be used to consider those that naturally group themselves.

All analyses will be performed with a significance level of 0.05, and appropriate multiple comparisons adjustments will be performed as needed. Categorical variables will be described with counts and percentages, and analyzed using appropriate statistical methods, such as hypothesis tests or logistic regression models.

Discussion

Currently, scientific evidence regarding the medical management and treatment of acute patellar dislocations is sparse. As such, the standard of care for non-operative treatment is highly variable does not adequately address the biological or biomechanical mechanisms necessary to restore lower extremity function and protect the long-term health of articular cartilage following injury. A significant need remains to identify novel combinations of therapies that successfully restore function and preserve joint integrity. The goal of this trial is to combine 2 easily implementable therapies to evaluate if the combination significantly improves patient reported outcomes, function, and joint health over the first year of recovery.

Early aspiration and saline injection may decrease the pro-inflammatory environment associated with post-traumatic hemarthrosis thereby reducing pain and negative neuromuscular feedback associated with a joint effusion [5, 8]. While observing elevated inflammatory markers after acute injury is not surprising, the inflammation process is not benign. Cartilage degradation begins immediately after acute knee injury with significant increases in synovial biomarkers of collagen breakdown [5, 6]. Additionally, increased inflammatory cytokine and degradative enzyme concentrations after acute knee injury may contribute to both short- and long-term patient-reported outcomes. We will also be able to assess if a simple saline injection is able to potentially amplify the effect of BFRT while circumventing the negative impact associated with corticosteroid injections [17].

Blood-Flow Restriction Training is also a promising modality for patients who suffer patellar dislocations. We have previously shown that these individuals have clinically important impairments in quadriceps and hip strength as well as altered knee biomechanics compared to healthy volunteers [18]. Increased quadriceps strength has been shown to be protective against patellofemoral cartilage loss as well as improved pain and function [19]. Hip weakness and increased knee abduction angles may place the patient at greater risk for repeated lateral patellar dislocation or subluxation, and increases the compressive and shear forces born by the articular cartilage [19, 20]. BFRT allows the subject to exercise with light resistance to derive similar training benefits seen with higher intensity resistance exercises (Figure 2) [9-13, 21-24]. Potentially with BFRT the

negative morphological adaptations of hip and thigh musculature that result in abnormal lower extremity biomechanics can be addressed, while compressive and shear forces born by the patellofemoral articular cartilage are minimized thereby promoting recovery [14, 20].

We seek to address the shortcomings of the current treatment strategies by specifically addressing progressive cartilage degradation, muscle weakness, and functional impairment following acute first-time patellar dislocations. Current treatments do not address the posttraumatic inflammatory cascade after acute knee injury. We and others have shown that this corresponds with progressive cartilage degradation over time [6, 25]. In addition, current physical therapy protocols do not adequately restore quadriceps or hip muscle strength resulting in altered knee biomechanics. The combination of a pro-inflammatory intra-articular environment and persistent biomechanical deficits undoubtedly contribute to the high rate of PTOA after patellar dislocation. By addressing both biologic and biomechanical mechanisms of PTOA, the proposed interventions may alter the progression of PTOA in this high-risk patient population. The long-term impact of this study is that the progression of PTOA may be delayed or potentially even avoided. These results may then impact the treatment paradigms for other acute conditions such as anterior cruciate ligament injuries, shoulder dislocation, and/or ankle sprains.

Trial Status

This is protocol version 1.0 (February 6, 2020). Patient recruitment will begin in January, 2021 with recruitment ending December, 2023.

List of Abbreviations

(BRAINS) - Blood flow Restriction training, Aspiration, and Intra-articular Normal Saline
(BFRT) - blood-flow restriction training
(ACL) - anterior cruciate ligament
(PTOA) - post-traumatic osteoarthritis
(IL-1a) - interleukin-1a
(MMP-3) - matrix metalloproteinase-3
(VAS) - visual analog scale
(MRI) - Magnetic Resonance Imaging
(LOP) - limb occlusion pressure

(PTP) - personalized tourniquet pressure
(ANCOVAs) - analysis of covariance
(MANCOVAs) - multivariate analysis of covariance

Declarations

Ethics approval and consent to participate

All materials and methods regarding this study have been analyzed and approved by the Institutional Review Board at the University of Kentucky (IRB#: 56541). All procedures are in agreement with the principles expressed in the Declaration of Helsinki. Participants will be informed about the scope and procedures of the study and will be asked to sign an informed consent by a member of the research staff before starting the initial evaluation.

Consent for publication

Not applicable

Availability of data and materials

Data will be collected in a protected database with an unidentified ID number provided for each participant. Data are available on request by sending an email to Cale Jacobs. All data will be available for 5 years after the relevant publication.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The manuscript was written by Benjamin D. Brightwell, Cale Jacobs, and Brian Noehren. Kathrine Thompson organized the statistics plan. All the authors participated in conceptualization of the protocol, developed methods, critically read, improved, and approved the final manuscript.

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Not applicable

Biological Specimens

Laboratory analyses of biologic samples outcomes: Data sheets will record descriptive information on the biopsy when collected (number of tubes, etc.). Samples will be labeled according to the visit the study participant attended. The sample tubes will be labelled with the participant's study ID number first. For example, when collecting data subject 05 on visit 2, the images will be labelled as: PI05_V2 followed by the type of fluid. For biologic samples, similar identifiers will be used with _urine or _serum used to identify the type of fluid (example: PI05_V2_urine).

Blood samples: Standard venipuncture will be used to collect 10 mL blood samples at each of the five study visits. The PI and research coordinator have both completed the UK Phlebotomy Class and completed the “Phlebotomy Clinical Training and Competency Validation” form to allow drawing blood samples from study subjects. In addition, the 4 other research coordinators in the Department of Orthopaedic Surgery and Sports Medicine have also been trained and certified in phlebotomy. While not key personnel in the current study, they will be added to the study personnel list to act as back-ups should both the study coordinator and PI not be available to perform the study blood draws.

Urine samples: Similarly, urine samples will be collected at all 5 study visits. The Functional Orthopedics Assessment Laboratory (FOAL) is located within the clinical space at the UK Orthopaedic and Sports Medicine

Center. There is a dedicated, lockable restroom located next door to the FOAL which allows participants a private area to provide a urine sample, and the sample can then be discreetly transferred from the restroom to the FOAL.

Sample processing: Blood and urine samples will be collected at all study time points. Serum and urine samples will be initially processed in the FOAL. Blood and urine samples will be spun in a refrigerated centrifuge at 3500 RPM for 10 minutes. Serum and urine will then be aliquoted into separate pre-labeled cryovials. Samples will be initially stored on site at -80°C in a freezer, and subsequently transferred from the clinical facility to the University of Kentucky Orthopaedic Biomarker Repository for analysis (UK's Charles T. Wethington Building, Room 443) on a monthly basis.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the UK Orthopedic Biomarker Repository. These samples could be used to research the causes of osteoarthritis after meniscus injury, its complications and other conditions for which individuals with meniscus injuries are at increased risk, and to improve treatment. The UK Orthopedic Biomarker Repository (CTW 443) will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio-sample storage may not be possible after the study is completed.

When the study is completed, access to de-identified study data and/or samples will be available from the principal investigator on reasonable request.

At the conclusion of the study, biologic samples will be analyzed in the UK Biomarker Analysis Laboratory.

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