Vibratory Stimuli: A Novel Rehabilitation Method for Preventing Post-Traumatic Knee Osteoarthritis

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PROTOCOL TEMPLATE: INTERVENTIONAL STUDY

Complete Title: Vibratory Stimuli: A Novel Rehabilitation Method for Preventing Post-Traumatic Knee Osteoarthritis

Short Title: Vibration and Knee Osteoarthritis

Drug or Device Name(s): whole body vibration, local muscle vibration

FDA IND/IDE (if applicable): IDE granted by UNC-Chapel Hill Biomechanical IRB (IRB# 15-0838)

Sponsor: US Department of Defense

Protocol Date: 5/18/2015

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
CAR	Central activation ratio
HST	Heelstrike transient
LMV	Local muscle vibration
OA	Osteoarthritis
vGRF	Vertical ground reaction force
WBV	Whole body vibration

PROTOCOL SYNOPSIS

Study Title	Vibratory Stimuli: A Novel Rehabilitation Method for Preventing Post-Traumatic Knee Osteoarthritis
Funder	US Department of Defense
Clinical Phase	Phase II
Study Rationale	Anterior cruciate ligament injury and reconstruction surgery (ACLR) dramatically increase the risk of developing knee osteoarthritis (OA). Individuals with ACLR possess deficits in quadriceps muscle function and proprioception (joint position sense) that alter knee joint loading during tasks such as walking in manners that contribute to development of knee OA. Vibratory stimuli enhance quadriceps function and proprioception and may, therefore, reduce the risk of knee OA. The purposes of this study are to 1) evaluate and compare the effects of whole body vibration (WBV) and local muscle vibration (LMV) on quadriceps function, knee joint proprioception, and walking gait biomechanics in individuals with ACLR and 2) identify characteristics that determine the efficacy of WBV and LMV for improving quadriceps function, knee joint proprioception, and walking gait biomechanics in individuals with ACLR.
Study Objective(s)	Primary • To determine the effects of WBV and LMV on quadriceps function, proprioception, and gait biomechanics in individuals ACLR • To compare the effects of WBV and LMV on quadriceps function, proprioception, and gait biomechanics in individuals ACLR • To identify factors that predict the effects of LMV and WBV on quadriceps function, proprioception, and gait biomechanics in individuals ACLR
Test Article(s)	WBV or LMV delivered at a frequency of 30Hz and intensity of 2*g*
Study Design	This preclinical investigation will utilize a single-blind randomized controlled experimental design whereby 75 individuals with primary unilateral ACLR will be randomly assigned to WBV, LMV, and Control groups. Stratified randomization into 3 groups of equal size (n = 25) will be performed using a computer generated randomization algorithm to ensure stratification with respect to age and time since ACLR.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria 1. Subjects age 18-35

	2. Undergone primary unilateral ACLR within 6 months to 5 years of participation 3. Knee Injury and Osteoarthritis Outcome Score (KOOS) self-report survey Pain subscale score > 53.1 and Symptom subscale score > 44.9 4. Cleared by physician to resume physical activity, and currently physical active at least 20 minutes 3x per week 5. Quadriceps central activation ratio < 95% Exclusion Criteria 6. History of ACL graft rupture 7. History of neurological disorder 8. History of musculoskeletal injury to either leg within the 6 months prior to participation 9. Pregnant or planning to become pregnant
Number Of Subjects	75
Study Duration	Each subject's participation will last approximately 3 hours and 45 minutes over approximately 2 weeks. The entire study is expected to last 3 years.
Study Phases Screening Study Treatment Follow-Up	(1) Screening: screening for eligibility and obtaining consent and (2) Intervention: study intervention/experimental treatment. Phase 2 will involve 2 testing sessions separated by approximately 1 week.
Efficacy Evaluations	1. Gait biomechanics (vertical ground reaction force linear and instantaneous loading rates, peak internal knee extension moment, peak internal knee valgus moment) 2. Somatosensory function (knee joint position sense error) 3. Quadriceps function (isometric peak torque)
Statistical And Analytic Plan	Pre-Post change scores for each of the primary outcomes will be compared between groups via one-way ANCOVA
DATA AND SAFETY MONITORING PLAN	David Berkoff, MD from the UNC-Chapel Hill Department of Orthopaedics will serve as the Research Monitor for this investigation. The PI will provide the Research Monitor a summary report during each quarter of the funding period that details information detailing enrollment, verification of informed consent, and adverse event documentation. The Research Monitor's primary responsibilities relate to the proper conduct of the investigation and the welfare of the subjects who are involved. As such, Dr. Berkoff will have the authority to suspend research associated with the project in the event of violations of study protocol.

1 BACKGROUND AND RATIONALE

1.1 Introduction

Osteoarthritis (OA) is the most common cause of medical discharge from military service during peacetime and the second most prevalent cause during armed conflict, ranking it as one of the largest military "force subtractors".[1] Traumatic knee injuries are of particular concern, as they almost universally result in post-traumatic OA in military personnel.[2] Knee injuries comprise 19% of all injuries sustained during military training[3] and 15% of all non-combat injuries during deployment.[4] Additionally, knee injuries are the third most prevalent type of injury leading to battlefield evacuation, and Rivera et al.[2] reported that 100% of knee injuries sustained during combat resulted in OA.

Anterior cruciate ligament (ACL) injury dramatically increases the risk of developing knee OA.[5] ACL injury also accelerates knee OA development, as radiographic evidence of OA has been identified as early as 5 years following injury.[6] While surgical reconstruction (ACLR) is the standard of treatment and improves joint stability, ACLR does not reduce the risk of developing knee OA.[7] Therefore, *ACLR represents an ideal model for evaluating novel rehabilitation techniques for preventing development of post-traumatic knee OA*.

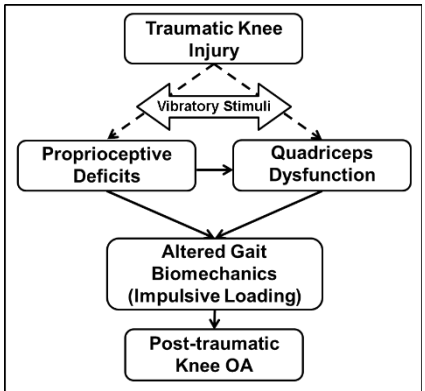


Figure 1: Knee injuries lead to proprioceptive deficits and quadriceps dysfunction. These factors alter gait biomechanics in manners which contribute to development of post-traumatic knee OA. Vibratory stimuli may prevent these negative effects, thus mitigating the risk of post-traumatic knee OA.

Impulsive/high rate joint loading contributes to the development of knee OA.[8, 9] Quadriceps dysfunction/weakness is a highly common, lingering complication associated with ACLR and other traumatic knee injuries that is caused by a neuromuscular phenomenon known as arthrogenic muscle inhibition (AMI).[10] Because the quadriceps functions as a shock absorber in the early stance phase during walking and running gait, quadriceps dysfunction results in impulsive loading of the knee joint as evidenced by higher loading rates.[11, 12] Given the repetitive nature of gait and its integral role in human locomotion, this impulsive loading contributes to development of OA.[8, 9] Recent evidence suggests that that quadriceps dysfunction associated with ACLR results in joint space narrowing, a radiographic indicator of knee OA.[13] Individuals with traumatic knee injuries also display sensory/proprioceptive deficits[14, 15] which magnify quadriceps dysfunction[16] and contribute to impulsive loading.[17, 18] As such, treatments that improve quadriceps function and proprioception may reduce the risk of developing post-traumatic knee OA (Figure 1).

1.2 Name and Description of Investigational Product or Intervention

Whole Body Vibration (Power Plate pro5)

Local Muscle Vibration (prototype stimulator – IDE granted by UNC-Chapel Hill Biomedical Institutional Review Board)

1.3 Non-Clinical and Clinical Study Findings

Quadriceps strengthening is an inherent component of rehabilitation of ACLR and other traumatic knee injuries, but is commonly ineffective due to the fact that the underlying neural deficiencies (i.e. AMI) are not addressed by conventional approaches.[10, 19, 20] However, both direct (local muscle vibration - LMV) and indirect (whole body vibration - WBV) vibratory stimuli enhance quadriceps function in individuals with non-pathological knees,[21-23] and may minimize the negative effects of AMI. We demonstrated that LMV enhances quadriceps function in healthy individuals,[23] and that both WBV and LMV produce

equivalent improvements in quadriceps function following experimental knee joint effusion (i.e. simulated knee trauma) in healthy individuals.[24] Vibratory stimuli also improve proprioception,[25, 26] and we demonstrated that improving knee proprioception decreases impulsive loading during walking gait in individuals diagnosed with knee OA.[27, 28] *These findings suggest that vibratory stimuli may improve quadriceps function, proprioception, and gait biomechanics (e.g. impulsive loading) following traumatic knee injuries, potentially reducing the risk of developing knee OA*.

Our preliminary data and findings reported by other researchers[14, 25, 26, 29] support our hypothesis that vibratory stimuli may enhance rehabilitation of traumatic knee injuries. These studies indicate that incorporation of vibratory stimuli into ACLR rehabilitation improves postural stability, quadriceps strength, and proprioception.[14, 25, 26] Additionally, a recent animal model demonstrated that WBV minimized articular cartilage loss in rats with knee OA caused by ACL transection.[29] However, *the effects of vibratory stimuli on factors linked to the development of post-traumatic knee OA have yet to be investigated*.

Clinical application of WBV may be limited, as these devices require a fixed location, permit limited types of rehabilitation exercises due to the restricted space of the device (~5 ft^2), and may be cost-prohibitive (as much as $10,000). However, LMV can be integrated into a portable, cost-effective device (~$250) for use in a variety of rehabilitation tasks and settings. LMV may also be more effective, as it is applied directly to the quadriceps, thus it is less susceptible to damping of the vibratory stimulus as it passes through the lower extremity such as occurs with WBV.[30] However, *it is unclear if WBV and LMV have similar effects on quadriceps function, proprioception, and gait biomechanics in individuals with traumatic knee injuries.*

The results of this investigation will provide "proof of concept" regarding the utility of WBV and LMV for prevention and management of knee OA, and will advance our understanding of the development and progression of this disease. Traditional rehabilitation and treatment methods have been only moderately effective due to the fact that AMI limits the efficacy of quadriceps strengthening by preventing adequate activation. Therefore, the results of this investigation may promote the development of improvements in patient care by supporting a shift in the treatment of knee pathologies (i.e. by demonstrating that AMI should be addressed before attempting to strengthen the quadriceps to enhance traditional rehabilitation). As knee OA adversely affects quality of life, the improved ability to treat and prevent knee OA resulting from this investigation would lead to improvements in quality of life. This information would also inform the development of a larger, long-term clinical trial to evaluate these effects on the long-term health and clinical outcomes in individuals who are afflicted with knee OA or are at heightened risk for development of post-traumatic knee OA. These outcomes would have a direct impact on the substantial burden of knee OA on the US health care system.

Exercise in general, including rehabilitation exercise, carries the risk of injury, pain, and soreness/discomfort. However, the tasks subjects will be asked to perform in this investigation are common to activities of daily living and rehabilitative exercise (i.e. quadriceps contractions, squatting, and walking), and strength training, and do not present increased risk of adverse events compared to these same risks when these activities are performed outside the laboratory setting (i.e. rare). The risk of subjects experiencing mild discomfort for a brief period of time (less than 1 second) during the electrical stimulation used for the Quadriceps Function Assessment is very common. However, this discomfort will immediately cease, and subjects will be familiarized with the electrical stimulation before

the testing procedure begins. Exposure to vibration may infrequently cause itching in the lower extremity and dizziness, both of which typically subside within minutes following exposure.

1.4 Relevant Literature and Data

We have conducted a series of investigations that support the rationale for the proposed investigation and demonstrate our ability to conduct the proposed RESEARCH STRATEGY. Each study is described below.

1. LMV enhances quadriceps function several minutes following application. We evaluated the effects of LMV on quadriceps activity in *healthy individuals with non-pathological knees* (n=22).[23] Quadriceps activity (electromyographic amplitude) was measured during maximal isometric contractions prior to and immediately, 5, 15, and 30 minutes following LMV or a Control condition (no vibration). A custom-built device identical to what we have proposed was used to deliver the LMV stimulus. LMV enhanced quadriceps activity, and this effect persisted for several minutes following application (Figure 2). *These findings support our hypothesis that LMV enhances quadriceps function for a sustained period of time*. It is likely that these healthy individuals were subject to a "ceiling effect" regarding improvements in maximal quadriceps activity. This suggests that LMV has a robust neuromuscular effect, thus we anticipate that individuals with knee pathologies who possess deficits in quadriceps function (e.g. ACLR) will realize larger improvements in quadriceps function compared to the healthy individuals in this preliminary study.

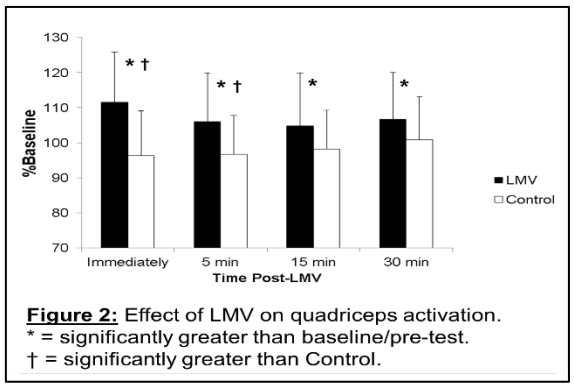


Figure 2: Effect of LMV on quadriceps activation.
* = significantly greater than baseline/pre-test.
† = significantly greater than Control.

2. WBV and LMV enhance quadriceps function similarly in individuals with simulated knee trauma. We evaluated the effects of WBV and LMV on quadriceps function in *healthy individuals with simulated knee trauma* (n=43).[24] The underlying cause of quadriceps dysfunction, AMI, is attributable to sensory information that signals pathology including pain, inflammation, swelling, and damage to mechanoreceptors.[31] AMI can also be induced experimentally by injecting saline into the knee joint which mimics the effects of swelling/effusion.[32] Quadriceps function was assessed via the central activation ratio (CAR). CAR quantifies an individual's ability to voluntarily activate a muscle, and is an indicator of AMI. A detailed description of this method is provided in the RESEARCH STRATEGY below. Following pre-test measures, 60mL of saline was injected into the knee joint space to induce AMI. Subjects were then exposed to WBV, LMV, or no vibration (Control), and quadriceps function was reassessed post-intervention. The interventions and methods for assessing quadriceps function utilized in this preliminary study are identical to those proposed in the RESEARCH STRATEGY. CAR improved significantly with WBV (+8.3%) and LMV (+5.9%), but not in the Control group (+0.7%). While both forms of vibration improved quadriceps function, this improvement did not differ between LMV and WBV. Additionally, subjects who experienced the greatest inhibitory effects of effusion displayed the greatest improvements in quadriceps function with vibratory stimuli. *These findings support our hypothesis that WBV and LMV may enhance quadriceps function similarly in individuals with knee pathology*. We

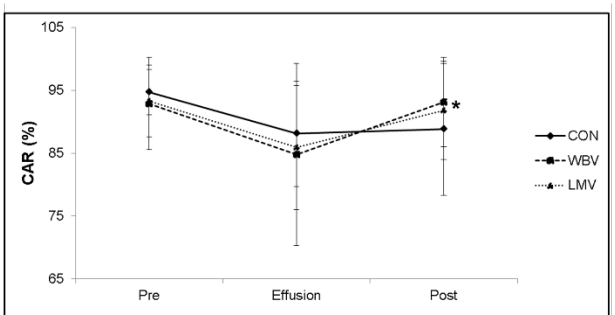


Figure 3: LMV and WBV improved quadriceps activation similarly following knee effusion, but no improvement occurred in the Control group.
* = Significant improvement vs. Effusion.

anticipate that individuals with "real" knee pathologies (as opposed to the acute, simulated trauma in this preliminary investigation) will realize substantially larger improvements in quadriceps function due to the chronic nature of their quadriceps dysfunction.

3. Treatment modalities that improve proprioception may reduce impulsive loading. We evaluated the effects of stochastic resonance electrical stimulation (SR) on proprioception and gait biomechanics in *individuals with knee OA* (n=52).[27, 28] Impulsive loading was quantified from the loading rates of the peak vertical ground reaction force (vGRF) and heel strike transient (HST). The HST is a rapid, transient rise in the vGRF which occurs shortly following ground contact during gait that is indicative of impulsive loading.[11, 12] SR improved proprioception and altered gait biomechanics in manners that may slow knee OA progression. Specifically, SR increased the knee flexion angle at ground contact, decreased quadriceps/hamstring coactivation, and decreased impulsive loading (Figure 4). *These findings demonstrate that modalities that improve proprioception potentially reduce impulsive loading*. We anticipate that WBV and LMV will both improve proprioception in individuals who have undergone ACLR, thus altering gait biomechanics in manners that would reduce the risk of developing knee OA.

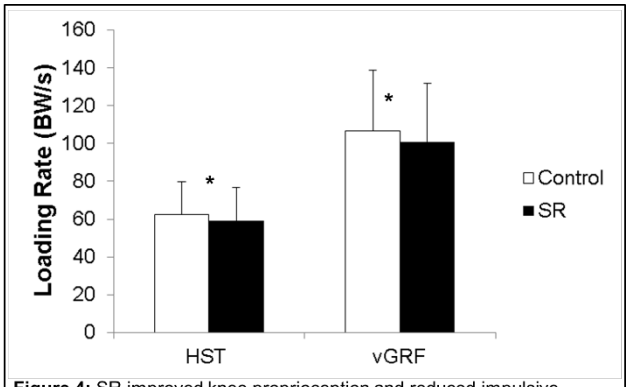


Figure 4: SR improved knee proprioception and reduced impulsive loading as evidenced by significant*decreases in the loading rates (Body Weight/s) of the heel strike transient (HST) and peak vertical ground reaction force (vGRF) compared to the Control/no SR condition.

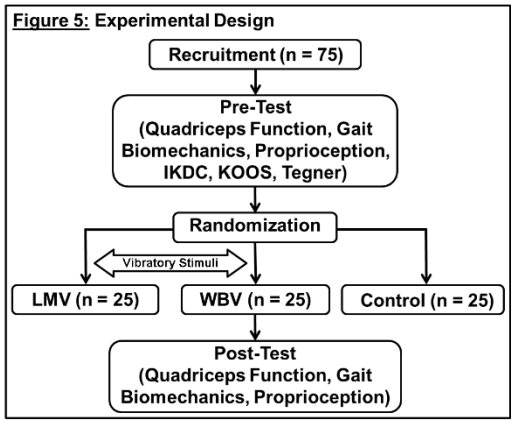
2 STUDY OBJECTIVE

The *long-term objective* of this line of research is to improve rehabilitation of traumatic knee injuries and prevent post-traumatic knee OA. The *objectives of this proposal* are to 1) determine the acute effects of WBV and LMV on quadriceps function, proprioception, and gait biomechanics in individuals who have experienced traumatic knee injury (ACLR); 2) compare the efficacy of LMV and WBV for these purposes; and 3) identify factors which predict the efficacy of these modalities.

3 INVESTIGATIONAL PLAN (brief overview)

3.1 Study Design

This preclinical investigation will utilize a single-blind randomized controlled experimental design whereby 75 individuals who have undergone ACLR will be randomly assigned to WBV, LMV, and Control groups (Figure 5). This convenience sample will include individuals recruited from two local orthopaedic clinics (UNC Department of Orthopaedics and Triangle Orthopaedic Associates), local rehabilitation clinics, and the University population, as well as veterans recruited from the Veterans Affairs Medical Center in nearby Durham, NC. Quadriceps function, proprioception, and walking gait biomechanics will be assessed prior to and following vibratory treatments (LMV or WBV) or a Control intervention. The WBV and LMV groups will



receive a single session of vibratory stimuli which we previously demonstrated to enhance quadriceps function.[23, 24] The Control group will perform identical procedures, but no vibratory stimulus will be applied.

3.2 Allocation to Treatment Groups and Blinding (if applicable)

Stratified randomization into 3 groups of equal size (n = 25) will be performed using a computer generated randomization algorithm. This algorithm will ensure stratification with respect to age and time since ACLR.

3.3 Study Duration, Enrollment and Number of Subjects

We anticipate that the entire study will last approximately 3 years. Each subject's participation will last approximately 3 hours and 45 minutes over approximately 2 weeks.

3.4 Study Population

We will recruit subjects who meet the following criteria:

1) age 18-35 years
2) undergone unilateral ACLR within 5 years prior to participation
3) at least 6 months post-ACLR
4) no history of ACL graft rupture or revision surgery
5) no history of neurological disorder
6) no history of injury to either leg within 6 months prior to participation (other than the initial ACLR)
7) Knee Injury and Osteoarthritis Outcome Score (KOOS) self-report survey Pain subscale score > 53.1and Symptom subscale score > 44.9
8) cleared by a physician for return to physical activity, and currently physically active, participating in at least 20 minutes of physical activity 3x per week.

Age will be restricted to 18-35 years as this age group is at the greatest risk of ACL injury[33] but is unlikely to possess idiopathic/non-traumatic knee OA.[34] The post-ACLR interval (6 months-5 years) will ensure that subjects are outside the acute inflammatory phase and reduce the likelihood that they have already developed post-traumatic knee OA. A history of graft rupture or bilateral ACLR may infer inadequate rehabilitation or flawed surgical procedures, and may alter the dependent variables. Neurological disorders, acute orthopaedic injuries, and high-level pain and symptoms in the ACLR limb may also influence the dependent variables. The criterion values for the KOOS subscale scores are based on reference values obtained from more than 4,000 individuals 1 and 2 years post-ACLR.[35] Lastly, sedentary individuals may develop knee OA via other mechanisms (e.g. compromised waste-nutrient exchange) rather than the hypothesized loading mechanisms.

Though highly prevalent, not all individuals display quadriceps dysfunction following ACLR.[10, 36-38] We hypothesize that individuals who do not display quadriceps dysfunction are less likely to develop post-traumatic knee OA, and would receive limited benefits from vibratory stimuli. Self-report surveys, including the KOOS, will always be assessed first followed immediately by quadriceps function. In the event that subjects do not possess quadriceps dysfunction (i.e. CAR < 95%),[10, 38] they will be excluded from the investigation. These procedures will ensure that we enroll the target population.

4 STUDY PROCEDURES (what will be done)

Subjects will report to the UNC Neuromuscular Research Laboratory for three separate sessions. During Session 1, subjects will complete the approved informed consent document, as well as the Self-Report Surveys, Gait Biomechanics Assessment, and Quadriceps Function Assessment described below. These procedures will be used to determine if subjects meet the inclusion criteria, familiarize the subject with the testing procedures, and establish parameters necessary for the subsequent testing sessions to expedite data collection. Upon reporting to the laboratory for Session 2, subjects will perform a 5 minute warm up on a stationary cycle ergometer at a self-selected pace to reduce the likelihood of injury. They will then be fitted with motion capture markers and electromyography (EMG) electrodes followed by the Gait Biomechanics and Quadriceps Function assessments. They will then perform the respective intervention to which they have been assigned, followed by post-test measures of the aforementioned assessments. Procedures for Session 3 will be identical with the exception that the Proprioception/Sensory Assessment described below will be performed prior to and following the interventions. Sessions 2 and 3 will be separated by 1-week washout periods, and the order of these sessions will be counterbalanced.

4.1 Screening/Baseline Visit procedures

Gait Biomechanics Assessment

Subjects will walk forward along a 6m (~20 ft) walkway at a comfortable, self-selected "fast" speed while biomechanical data are collected.[27, 39, 40] At least 5 practice trials will be performed during the familiarization session (Session 1) to determine the average preferred speed and ensure subjects can consistently strike a force plate mounted in the walkway with the test limb without noticeably altering their gait (i.e. "aiming" for the force plate). Gait speed will be monitored via an infrared timing system to ensure each trial is within ±10% of the preferred speed. Kinematics (knee motion patterns), kinetics (knee joint moments and ground reaction forces) and lower extremity muscle activity (quadriceps and hamstrings EMG) will be sampled during each trial. Subjects will perform 5 valid trials from which gait biomechanical variables will be averaged for statistical analysis.

EMG electrodes will be placed over the back (hamstrings muscles) and front (quadriceps muscles) of the thigh via adhesive interfaces. Electrode placement sites will be shaved, lightly abraded, and cleansed with isopropyl alcohol to improve adhesion to the skin and signal quality. Motion capture markers will be secured on the trunk and pelvis, and the thigh, shank, and foot segments via double-sided tape. All measurement hardware will be further secured via hypoallergenic tape.

Quadriceps Function Assessment

Subjects will be seated on a device used to measure muscle strength called an isokinetic dynamometer. Straps will be used to secure the torso, thigh, and lower leg to the device with the knee in 60° of flexion. The moveable arm of the dynamometer will be fixed in place. Two adhesive stimulating electrodes will be placed on the anterior thigh over the quadriceps muscle. Subjects will be asked to contract the quadriceps maximally and as quickly as possible by "kicking out" against the dynamometer in response to a visual (light) stimulus while torque data are sampled. An investigator will view the torque data in real time and apply an electrical stimulus to the quadriceps after the torque reaches a maximal plateau. This electrical stimulus will consist of a 10 pulse train, pulse duration of 0.6ms, delivered at a frequency of 100Hz, and an intensity of 125V. The electrical stimulator will be isolated from fluctuations in building's electrical power supply via a stimulus isolation unit. These methods and stimulus characteristics replicate those of previous investigations conducted in healthy[41-43] and pathological[20, 44-

[46] populations, including the recent investigations conducted in our laboratories noted above. Quadriceps AMI will be quantified via peak torque (PT), rate of torque development (RTD), and the central activation ratio (CAR) during these maximal contractions. Measuring the CAR involves applying an electrical stimulus to a maximally contracting muscle (superimposed burst) which activates all the muscle's motor units. The ratio of torque resulting from the superimposed burst to the maximal voluntary torque represents the level of inhibition.[20] Subjects will perform at least 2 practice trials to become familiar and comfortable with these procedures. Three trials will then be recorded from which PT, RTD, and CAR will be averaged for statistical analyses.

Proprioception/Somatosensory Assessment

Proprioceptive/Somatosensory function will be assessed via a partial weight-bearing joint repositioning task.[28, 47] Subjects will be positioned supine on a sliding platform that will be reclined 75° relative to the vertical (Figure 5, Appendix A). This platform will permit unrestricted knee motion, but will control extraneous factors that influence joint position sense assessment during weight-bearing such as postural sway and trunk position. Subjects will be blindfolded, and each trial will begin with the knee in full extension, and subjects will flex the knee to a prescribed angle (reference angle) by sliding the platform downward. This angle will be maintained for 5s after which the subject will return to full knee extension, and will then attempt to replicate the reference angle. The absolute difference between the reference angle and the reproduced angle will be calculated and averaged across 5 trials for statistical analyses. Knee joint angles will be assessed via an electrogoniometer placed over the knee and secured using hypoallergenic double-sided tape.

We will also measure vibratory perception threshold (VPT), a more clinically feasible assessment of somatosensory function. Deficits in VPT have been identified in individuals with knee pathologies and are associated with impulsive loading during gait.[18, 48] VPT is measured using a device called a biothesiometer which vibrates at varying amplitudes that are controlled by the investigator. VPT will be assessed by placing the biothesiometer on bony prominences at the medial and lateral femoral epicondyles, medial (tibial) and lateral (fibular) malleoli, and 1st metatarsophalangeal joint.[18, 48] The amplitude of the vibration will be increased gradually, and subjects will verbally indicate the point at which they consciously perceive the vibratory stimulus, and the corresponding amplitude will be recorded as VPT. Three trials will be performed at each site and averaged for statistical analysis.

Self-Report Surveys

The International Knee Documentation Committee Subjective Knee Form (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Tegner Activity Scale self-report surveys will be used to document subjects' knee trauma history, current symptoms, and functional ability. The IKDC and KOOS have been demonstrated as valid indicators of knee function and clinical outcomes in individuals with knee pathologies,[49, 50] while the Tegner scale is a valid indicator of physical activity level in these individuals.[51] These surveys will be administered electronically via Qualtrics.

4.2 Intervention/Treatment procedures

Vibratory Interventions

All interventions will be performed with subject standing on a WBV device in approximately 40° of knee flexion, but the WBV device will only be "on" for the WBV group. Subjects assigned to the WBV group will receive a vibratory stimulus (30Hz, 2*g*) applied for 1 minute. This exposure will be repeated 6 times with 2 minutes of rest between exposures. Subjects in the LMV group will receive an identical stimulus (30Hz, 2*g*) via a custom-built vibrator secured over the distal anterior thigh. We have previously

demonstrated that these interventions enhance quadriceps activity. Subjects in the Control group will perform these exact same procedures with the exception that no vibratory stimulus will be applied. All interventions will be conducted by a graduate research assistant, and the PI will blinded to group assignment.

4.3 Follow- up procedures (by visits)

None

4.4 Unscheduled visits

None

4.5 Subject Completion/ Withdrawal procedures

Subject participation in the study will be complete when he/she has completed Session 3. Subjects will receive prorated monetary compensation at this time.

4.6 Screen failure procedures

All subjects will provide informed consent prior to engaging in the screening procedures. Potential subjects who complete the screening session but do not meet the inclusion criteria will be thanked for their time and excluded from further participation.

5 STUDY EVALUATIONS AND MEASUREMENTS (how measurements will be made)

See 4.1 Screening/Baseline Visit procedures

5.1 Safety Evaluations

All data will be deidentified. Subjects will be identified only by a subject ID# to which their personal information will not be linked. Deidentified data files (e.g. gait biomechanics data trials) will be stored and backed up in numerous password-protected locations including computers in the Neuromuscular Research Laboratory, external hard drives, and the UNC-CH Research Computing Mass Storage System.

David Berkoff, MD from the UNC-Chapel Hill Department of Orthopaedics will serve as the Research Monitor for this investigation. Dr. Berkoff possesses both the research ethics and medical expertise necessary to carry out this role. The PI will provide the Research Monitor a summary report during each quarter of the funding period detailing the information that is necessary for Dr. Berkoff to perform his duties. These duties will include ensuring subjects meet the enrollment criteria, verifying the informed consent process for each subject, and monitoring adverse events. A detailed description of the Research Monitor's duties and authorities (i.e. conditions under which the Research Monitor can suspend research activities) has been uploaded in IRBIS.

Prior to analysis, the data will be screened for outliers (values more than 3 sd beyond the mean) and evaluated for normality via the Shaprio-Wilk test, visual inspection of the histograms, and evaluation of the ratios of the skewness and kurtosis statistics to their standard errors to ensure quality.

The 5-minute warm-up prior to testing is designed to reduce the risk of muscle soreness and/or injury during testing. The electrical stimulator used for the Quadriceps Function Assessment will always be connected to a stimulus isolation unit to ensure that the subject is isolated from fluctuations in the building's power supply. Any safety concerns (i.e. musculoskeletal injury) would likely be recognized immediately during testing, but subjects will be instructed via the informed consent document that they should inform UNC Student Health Services or their personal physician in the event that they experience lingering issues after leaving the laboratory.

All members of the research team involved with data collection are certified in CPR and First Aid. These individuals will monitor subjects for adverse events during testing, and will refer any individuals who experience adverse events to the Stallings-Evans Sports Medicine Center (located in the building adjacent to Fetzer Hall where the Neuromuscular Research Laboratory is located), UNC Student Health Services, or Emergency Medical Services depending on the nature and severity of the adverse event.

6 STATISTICAL CONSIDERATION

6.1 Primary Endpoint

This pre-clinical trial will evaluate the acute effects of the interventions, thus the immediate post-test assessment will serve as the primary endpoint.

6.2 Statistical Methods

Specific Aim 1: To determine the effects of WBV and LMV on quadriceps function, proprioception, and gait biomechanics in individuals with ACLR.

Analyses for Aim 1 will be performed using pre-post change scores for quadriceps function, proprioception, and gait biomechanics as dependent variables in separate statistical models. Mean change scores will be compared across groups (WBV, LMV, and Control) via one-way analysis of covariance (ANCOVA). Dunnett's procedure will be used to evaluate each the least-squares means for each of the intervention arms (WBV and LMV) versus control in a relatively powerful manner while controlling the overall significance level at two-sided 0.05. The corresponding pre-test values for each dependent variable will be managed as a covariate in these models to increase precision of the treatment effects, as well as to account any random imbalances among the groups with respect to these pre-scores. Other covariates would include variables with random imbalances across the groups measured at the pre-test.

The number of individuals who display HST prior to and following the intervention (or control) will be compared via McNemar's test. This analysis produces a χ^2 statistic for paired samples (i.e., the proportion with HST at pre-test vs. post-test, separately for each group).

Specific Aim 2: To compare the effects of WBV and LMV on quadriceps function, proprioception, and gait biomechanics in individuals with ACLR.

Aim 2 will be evaluated using the statistical models described above for Aim 1, but with focus on the statistical contrast of WBV versus LMV. Specifically, the pre-post change scores for each dependent

variable, adjusted for covariates, will be tested for the pairwise comparison of WBV versus LMV at the two-sided 0.05 significance level.

Specific Aim 3: To identify factors that predict the effects of LMV and WBV on quadriceps function, proprioception, and gait biomechanics in individuals with ACLR.

Aim 3 will be evaluated using multiple regression models. Pre-post change scores for each dependent variable will be included only for the WBV and LMV groups. We will then calculate simple correlations between these change scores and the pre-test values separately for quadriceps function, proprioception, and the KOOS. We hypothesize that individuals with greater quadriceps dysfunction and proprioceptive deficits combined with lower KOOS scores (i.e. greater pain, symptoms, etc.) will display greater improvements. Separately for each dependent variable, these variables will then be placed into a stepwise multiple regression model (starting with a forward selection step). In this way, the variable with the strongest relationship with the change score will be entered first, followed by the next strongest (after adjusting for the first), etc. The model selection will stop when no additional variables are identified to enter to leave the model at the 0.10 significance level. This less conservative significance level is selected to cast a wide net to include relevant candidate terms. Next, we will examine each of these terms, one-at-a-time, as an independent variable in another regression model where the change score is the dependent variable; an indicator term for the intervention (WBV vs. LMV) will also be included as an explanatory variable, as well as the interaction between the intervention indicator and the candidate term. The initial focus will be on the significance of the interaction term, as this will determine whether the effect of the candidate term is homogeneous (reflected by non-significance of the interaction at the 0.05 level) across the interventions, or not. If the test is non-significant, the interaction term will be removed and the model refitted; the candidate term is then assessed from this model regarding its ability to predict the homogeneous effect of LMV and WBV on the corresponding dependent variable. If the interaction test is instead statistically significant, then the interaction term is retained in the model, and statistical contrasts will be constructed to estimate and test the separate effects of the candidate term by intervention group.

6.3 Sample Size and Power

Quadriceps function is the primary outcome for this investigation, as it is the critical factor in controlling impulsive knee joint loading linked to development of post-traumatic knee OA. We conducted *a priori* power analyses[52] using data from our preliminary investigation involving these same vibratory stimuli following experimental knee joint effusion.[53] Pre-post change scores were calculated as described above in the statistical methods for Specific Aim 1, and effect size indices were calculated for one-way ANCOVA using pre-test scores as the covariate. These analyses indicate that a sample of 45-63 subjects (15-21 per group) would provide statistical power of 0.80 for $\alpha = 0.05$ to identify significant overall ANCOVA models for CAR ($f = 0.48$) and peak torque ($f = 0.41$), where f is the effect size calculated as the square root of the ratio of the between-group sum of squares and the error sum of squares. Further, these preliminary data generated the pairwise effect sizes presented in the table below calculated using the following equation:

$$\text{Effect Size} = \frac{[\Delta\text{WBV (or } \Delta\text{LMV)} - \Delta\text{Control}]}{\text{Pooled Standard Deviation}}$$

Effect Sizes for *Post Hoc* Group Comparisons of Pre-Post Change Scores

Quadriceps Function Variable	WBV vs. Control	LMV vs. Control	LMV vs. WBV
CAR	0.84	0.78	0.36
Peak Torque	0.98	0.70	0.35

Statistical power for the effect sizes given in Table 2 was calculated for one-tailed independent t-tests. These estimates indicate that a sample of 39-78 subjects (13-26 per group) would provide statistical power of 0.80 for $\alpha = 0.05$ to evaluate pairwise comparisons between the Control group and each vibratory intervention (i.e. Aim 1). In contrast, 194 subjects (97 per group) would be necessary to provide adequate power to identify the relatively small effect sizes for comparing the two vibratory interventions (i.e. Aim 2). The associated mean differences in CAR between WBV and Control and between LMV and Control were 8.26% and 5.86%, respectively, while the difference between LMV and WBV was only 0.68%. Similarly, the associated mean differences in peak torque between WBV and Control and between LMV and Control were 0.29 N/kg and 0.20 N/kg respectively, while the difference between LMV and WBV was only 0.04 N/kg. These data suggest that the small mean differences in the dependent variables between WBV and LMV, even when powered sufficiently, are not likely clinically or physiologically relevant. Therefore, we will recruit a sample of 75 individuals (25 per group) to address the proposed specific aims. This sample size will provide adequate power to demonstrate similar improvements in quadriceps function with WBV and LMV.

7 STUDY INTERVENTION (drug, device or other intervention details)

7.1 Whole Body Vibration

Whole body vibration will be delivered in this investigation via a commercially available device (Power Plate pro5). This device oscillates in the vertical dimension at a frequency of 30 Hz and acceleration of 2*g*.

7.2 Local Muscle Vibration

The local muscle vibration stimulator to be used in this investigation is a custom-built prototype developed in collaboration with the Department of Industrial and Systems Engineering at North Carolina State University as part of a collaborative grant to be used explicitly for the purposes of the proposed study. As of 5/13/2015, this device has been used to enhance muscle function via the exact intervention proposed for this study in more than 100 subjects in multiple previously approved studies with no adverse events. Furthermore, 25 of these subjects had undergone ACL reconstruction surgery and met the inclusion criteria for the proposed investigation.

This stimulator consists of a single-axis electromagnetic oscillator mounted on a plastic frame. The plastic frame was produced via 3D printing such that its under surface is curved to accommodate the shape of the anterior thigh. The electromagnetic oscillator consists of a standard audio speaker that is coupled with a frequency generator through an amplifier that causes it to vibrate in the anterior-posterior direction (i.e. into the quadriceps muscle). This vibratory stimulus is similar to the mechanics of a reflex hammer when evaluating the tendon-tap/knee-jerk reflex clinically in that it creates rapid changes in quadriceps length, thus exciting the muscle via the muscle spindle system. Vibration frequency is held

constant at 30Hz as determined by the frequency generator in the controller unit, and the acceleration is constrained to 2*g* via feedback provided to the controller unit from an accelerometer mounted on the oscillator.

8 STUDY INTERVENTION ADMINISTRATION(if applicable)

This preclinical investigation will utilize a single-blind randomized controlled experimental design whereby 75 individuals with primary unilateral ACLR will be randomly assigned to WBV, LMV, and Control groups. Stratified randomization into 3 groups of equal size (n = 25) will be performed using a computer generated randomization algorithm to ensure stratification with respect to age and time since ACLR. All individuals involved with data collection and analysis will be blinded to group allocation.

9 SAFETY MANAGEMENT

Research Monitor Responsibilities and Authorities

David Berkoff, MD from the UNC-Chapel Hill Department of Orthopaedics will serve as the Research Monitor for this investigation. Dr. Berkoff possesses both the research ethics and medical expertise necessary to carry out this role. The PI will provide the Research Monitor a summary report during each quarter of the funding period that details information necessary for him to perform the following responsibilities:

1. Enrollment data
    a. # of subjects (total and per group)
        i. The Research Monitor will be unblinded to group, but the PI and all research team members involved with data collection will remain blinded.
        ii. Groups will be identified by number only (e.g. Group 1 = Control, etc.) in reports generated by the PI, and the Research Monitor will be provided a key to decode group membership by the unblinded research assistants who are delivering the interventions.
        iii. The Research Monitor will evaluate enrollment data to ensure the enrollment rate is consistent with the project timeline (i.e. 30 subjects per year for Years 1 and 2; 15 for Year 3).

    b. The Research Monitor will verify subjects meet the enrollment criteria
        i. Relevant data regarding the inclusion/exclusion criteria (e.g. age, KOOS scores, CAR, time since ACL reconstruction surgery, etc.) will be entered in an electronic data management system (Epi Info, Centers of Disease Control and Prevention). This system is capable of generating spreadsheets for data organization. These spreadsheets will be provided to the Research Monitor to permit verification of the enrollment criteria.

2. Verify consent
    a. Data entry in Epi Info will require the member of the research team who is entering a given subject's data to verify (yes/no) that written informed consent was obtained. This individual will also be required to enter his/her initials in Epi Info to confirm that consent was obtained. The Research Monitor will verify that each subject has been consented based on these data contained in the quarterly report.

3. Monitor adverse events
    a. Subjects will be monitored for adverse events by the research team during data collection, and will be instructed to inform the research team immediately if they experience adverse events after leaving the laboratory. Information related to adverse events will be entered in Epi Info as described below.
        i. Adverse Event? (yes/no)
            1. If yes, was there appropriate follow up by research team?
                a. Subjects will be contacted within 1 day of identification of an adverse event and again after 1 week. The dates of follow up by the research team will be documented in Epi Info.
            2. Appropriate documentation sent to UNC-CH Biomedical IRB?
                a. The dates of submission, IRB response, and resolution will be documented in Epi Info.
            3. The Research Monitor will determine if the adverse event is associated with participation in the study using the UNC-CH Biomedical IRB decision tree (http://research.unc.edu/files/2012/11/ccm3_018993.pdf). Documentation (e.g. description of the adverse event, symptoms, etc.) will be sent to the Research Monitor for evaluation of risk which will be used to determine the following:
                a. Severity of the adverse event as per US Department of Health and Human Services guidelines (http://www.hhs.gov/ohrp/policy/advevntguid.html#AA)?
                b. Is this a recurring problem (i.e. multiple adverse events of the same type)?
                c. Is this adverse event specific to one of the interventions?

Authorities

The Research Monitor's primary responsibilities relate to the proper conduct of the investigation and the welfare of the subjects who are involved. As such, Dr. Berkoff will have the authority to suspend research associated with the project when any of the following occurs:

1. Enrollment criteria are inconsistent with those specified in the research protocol in 2 or more enrolled subjects in 2 consecutive quarters of the funding period
2. Written informed consent is not obtained for any subject in any quarter of the funding period
3. Failure by the research team to report any adverse event appropriately as per UNC-CH Biomedical IRB guidelines
4. Multiple adverse events are reported (3+) in a given quarter of the funding period
5. Multiple adverse events are reported within a given intervention group (5+) across the entire funding period

Any subjects who experience adverse events will be referred to UNC Student Health Services, the Stallings-Evans Sports Medicine clinic (located in the building adjacent to Fetzer Hall where the Neuromuscular Research Laboratory is located), or Emergency Medical Services depending on the nature and severity of the adverse event. All individuals involved with data collection are certified in CPR and First Aid.

10 DATA COLLECTION AND MANAGMENT

All data will be deidentified. Subjects will be identified only by a subject ID# to which their personal information will not be linked. Deidentified data files (e.g. gait biomechanics data trials) will be stored and backed up in numerous password-protected locations including computers in the Neuromuscular Research Laboratory, external hard drives, and the UNC-CH Research Computing Mass Storage System.

11 RECRUITMENT STRATEGY

The ACLR cohort for this investigation will consist of volunteers from the faculty, staff, and student populations at UNC-CH and the surrounding area. Potential subjects will be recruited verbally from classes following approval by course instructors. At this time, potential subjects will be read a standard recruitment script and will be allowed to ask any questions pertaining to the investigation. Individuals who are interested in participating will be provided the PI's contact information and asked to contact the PI to address any additional questions regarding the study and to schedule data collection. Additionally, subjects will be recruited via informational flyers posted on the UNC-CH campus and in local rehabilitation clinics, including the Durham VA Medical Center, and via an informational email posted on the UNC-CH server. Subjects will also be recruited from UNC Orthopedics (Jeff Spang, MD) and Triangle Orthopaedic Associates (Jeff Solic, MD). All subjects must receive physician approval to return to regular, unrestricted physical activity to be eligible for participation. Drs. Spang and Solic will provide subjects with information regarding participation in the study following the subject's clinical visit at which this approval is obtained. Dr. Kelli Allen (joint appointment at Durham VA Medical Center) will serve in this same capacity for recruiting subjects from the Durham VA Medical Center. We will also submit a request to the Carolina Data Warehouse for Health to generate a list of patients with ACL reconstruction within the past 5 years. This patient list will include names and multiple forms of contact information that will be used to contact potential subjects via telephone, letter/US Mail, or email depending on the available contact information to determine the individual's interest in participating in the study. Dr. Solic will perform similar retrospective chart reviews at Triangle Orthopaedic Associates to identify potential subjects. The Healthy Control cohort for this investigation will consist of volunteers from the faculty, staff, and student populations at UNC-CH and the surrounding area. Potential subjects will be recruited verbally from classes following approval by course instructors. At this time, potential subjects will be read a standard recruitment script and will be allowed to ask any questions pertaining to the investigation. Individuals who are interested in participating will be provided the PI's contact information and asked to contact the PI to address any additional questions regarding the study and to schedule data collection.

Drs. Spang and Solic each perform approximately 50 ACLR procedures annually, and each of their orthopaedic practices (UNC Orthopaedics and Triangle Orthopaedic Associates, respectively) performs more than 200 ACLR procedures annually. The Durham VA Medical Center performs approximately 10 ACLR procedures each year in veterans who meet the inclusion criteria. These data indicate that as many as 1,230 potential subjects will be available for recruitment via our clinical collaborations during the funding period (410/year x 3 years). Additionally, we will perform retrospective chart reviews in each of these clinical settings to identify potential subjects. Lastly, we will also recruit potential subjects from local rehabilitation clinics and from the University community. As part of ongoing research in our laboratories we have recruited 40+ individuals in the past year who meet these criteria from the University community alone without taking advantage of the aforementioned clinical collaborations that have been established for the project or targeting local rehabilitation clinics. As such, we are highly confident that we can recruit the necessary sample for the investigation.

12 CONSENT PROCESS

Upon reporting to the laboratory, and prior to screening and data collection procedures, all subjects will be required to read and sign the approved informed consent document. Members of the research team will oversee this process to ensure any questions subjects have are answered prior to providing written informed consent. Drs. Blackburn (PI), Padua (Co-Investigator), and Pietrosimone (co-investigator), and all research assistants will be obtaining consent. As the PI teaches courses in which potential subjects may be currently enrolled or enrolled in the future, these individuals will be informed that their participation or the lack thereof will not influence their academic standing. Similarly, UNC-CH employees will be informed that their participation or the lack thereof will not influence their employment status. Lastly, subjects recruited from orthopaedic and rehabilitation clinics will be informed their clinical care will not be influenced by their participation or the lack thereof.

13 PLANS FOR PUBLICATION

We intend to draft 3 primary manuscripts for publication that will detail, respectively, 1) the effects of the interventions on gait biomechanics, 2) the effects of the interventions on somatosensory function, and 3) patient characteristics that influence the efficacy of the interventions.

14 REFERNECES

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