Minimization of Quadriceps Dysfunction after Anterior Cruciate Ligament Injury

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SPECIFIC AIMS

ACL tears are common amongst the U.S. population, particularly in younger, physically active individuals, with approximately 300,000 tears occurring each year[1,2] at an annual cost estimated at $2.78 billion.[3] *Profound* quadriceps weakness and activation failure (i.e., the inability to completely activate the quadriceps muscle due to neural inhibition) usually develop rapidly after anterior cruciate ligament (ACL) injury and surgery.[4-6] Despite the significant progress made in ACL surgery and post-operative rehabilitation over the last few decades, most people have noteworthy quadriceps weakness and activation failure when they return to activity. Achieving quadriceps strength in the injured/reconstructed limb that is 90% of the uninjured side is considered important for realizing a successful outcome after ACLR,[7,8] however patients are often released from formal care and cleared to return to activity at values much lower than this criterion.[9-12] Our own work illustrates this point, with quadriceps strength in the ACLR knee averaging about 70% of the uninjured side at the time of physician clearance, with only 20% (13/66) of our patients achieving the recommended 90% quadriceps symmetry criterion.[11] Data from our laboratories and others show that quadriceps strength gradually improves over time, but rarely recovers completely even several years after the surgery.[6,13-15] This chronic quadriceps weakness significantly alters gait mechanics and contributes to knee instability, disability, and increased knee re-injury rate.[16-19] Although short-term patient-reported outcomes are very good after ACL reconstruction (ACLR), an *alarming number* (up to 50%) of the people sustaining this injury have clear evidence of post-traumatic osteoarthritis within 15 years of injury.[17,20,21] Altered movement patterns and abnormal joint loading due to poor quadriceps strength are theorized as the underlying cause of early post-traumatic knee osteoarthritis.[22-27] Indeed, prospective studies indicate that quadriceps weakness is directly associated with the onset of post-traumatic osteoarthritis after ACL injury and reconstruction.[28-30] Thus, interventions addressing quadriceps weakness are *critically* needed to optimally restore quadriceps strength after ACLR.

Resistance training is a powerful stimulus for improving muscle strength, quality, and function.[31-35] Indeed, we recently showed that high intensity eccentric training early after ACLR can induce meaningful improvements in quadriceps strength and voluntary activation.[34] While these improvements were paralleled by better movement profiles and biomechanical limb symmetry during functional tasks, recovery was still incomplete.[36] Thus, strength training alone is not sufficient to restore adequate quadriceps function. A key reason for incomplete recovery could be that interventions addressing strength and activation deficits seldom focus on restoring corticospinal function. This is critical because reduced excitability of spinal-reflexive and descending corticospinal pathways[37-39] have been attributed as potential sources of persistent quadriceps weakness after ACLR.[40,41] Our ***long-term goal*** is to develop an ACL rehabilitation intervention program that effectively minimizes post-traumatic knee osteoarthritis and promotes long-term health-related quality of life. It seems intuitive that normalizing quadriceps strength, neural excitability, and gait mechanics will be helpful. However, we currently do not know if it is possible to successfully address these issues with principles of operant conditioning. Thus, the *objective of this study is to perform a feasibility study to test the central hypothesis that operant up-conditioning of motor evoked responses can induce meaningful improvements in quadriceps strength and voluntary activation.*

STUDY AIMS AND HYPOTHESES

Specific Aim 1: Determine the feasibility of operant up-conditioning of motor evoked responses to improve quadriceps strength and voluntary activation in individuals with ACL reconstruction.

This *pilot* study will recruit thirty-two ACL-reconstructed individuals to study the feasibility of operant up-conditioning of motor evoked responses in restoring quadriceps strength and

activation. Subjects will either train to up-condition or not condition their motor evoked responses evoked by transcranial magnetic stimulation (TMS). Quadriceps strength and voluntary activation will be evaluated before, during, and after an eight-week intervention using the interpolated triplet technique.

Hypothesis 1a: Operant up-conditioning of motor evoked torque responses will result in significant improvements in quadriceps strength and voluntary activation.

Hypothesis 1b: Correlational analysis will show that individuals with greater ability to upregulate their corticospinal motor evoked torque responses will exhibit greater improvements in strength and activation.

Hypothesis 1c: The training-induced improvements in quadriceps strength and activation will peak at about 4-weeks and plateau after 6-weeks of intervention.

If successful, the results of the proposed studies will lay the foundation for future large scale studies to test the effectiveness of operant conditioning in mitigating chronic quadriceps dysfunction after ACL injury/surgery. The proposed study will also provide the much needed preliminary data for a competitive R01 application, where dosing and the effects of operant up-conditioning of motor evoked torque responses on quadriceps function, gait and risk of post-traumatic osteoarthritis using imaging-based biomarkers after ACL surgery will be studied in greater detail.

SIGNIFICANCE

ACL tears are common amongst the U.S. population, particularly in younger, physically active individuals, with approximately 300,000 tears occurring each year[1,2] at an annual cost estimated at $2.78 billion.[3] Despite restoration of knee stability through surgery and aggressive rehabilitation protocols designed to reestablish strength, quadriceps weakness is ubiquitous after ACLR. Poor quadriceps strength is a risk factor for altered movement patterns and asymmetrical limb-loading strategies,[36,42-44] during functional activities such as walking, landing, and stair descent.[36,45-48] Restoring quadriceps strength after ACLR is crucial as lingering quadriceps weakness has prospectively[29,30] and retrospectively[28,49] been linked to the post-traumatic osteoarthritis that affects 50% of ACLR knees 5-15 years after surgery.[50] Achieving quadriceps strength in the injured/reconstructed limb that is 90% of the uninjured side is considered important for realizing a successful outcome after ACLR,[7,8] however patients are often released from formal care and cleared to return to activity at values much lower than this criterion.[9-12] Our **own work** illustrates this point, with quadriceps strength in the ACLR knee averaging about 70% of the uninjured side at the time of physician clearance, with only 20% (13/66) of our patients achieving the recommended 90% quadriceps symmetry criterion.[11] *Thus, a paradigm shift is needed in the rehabilitation process to optimally restore quadriceps strength after ACLR.*

Significance of the proposed study and its potential to affect health care/clinical practice: Research focused on improving rehabilitation following ACLR is necessary as current rehabilitation fails to restore muscle strength, ultimately contributing to poor function, reduced quality of life, and the onset of osteoarthritis. While significant advances have been made in ACL surgical technique in the last decade[51], innovative approaches to improve post-surgical ACL rehabilitation have not yet been explored. The *permanent muscle weakness and muscle loss currently suffered by ACLR patients can undoubtedly be addressed* by changing the way we approach ACL rehabilitation. Embedding interventions into the current standard of care that are capable of directly addressing the source of muscle weakness will significantly improve our existing rehabilitation paradigm. The proposed research will strategically incorporate operant up-conditioning of motor evoked torque responses elicited by transcranial magnetic stimulation

to upregulate the functioning of the corticospinal pathways, thereby systematically addressing reduced corticospinal excitability after ACLR—which is a known source of quadriceps weakness— to improve knee strength and voluntary activation. Upon completion of this focused pilot trial, we will know whether operant conditioning of motor evoked torque responses is a feasible approach to improve quadriceps strength and voluntary activation. We will also gain knowledge regarding the optimal number of visits required to maximize treatment response, which is a critical element to identifying dose-response relationship. If successful, we will be able to expand upon the results of this study via an R01 application to perform a larger study with appropriate dose-matched control groups (e.g., TMS without conditioning paradigm), where comparative effectiveness and dosage of operant conditioning will be studied in greater depth. Thus, the proposed line of research will lead to an *evidence-based* approach to combatting the muscle weakness associated with ACL injury and reconstruction, which is desperately needed. We expect that upon completion of the proposed study, we will have laid a foundation for a novel rehabilitation approach that has the potential to eliminate chronic muscle weakness associated with ACLR.

INNOVATION

Our proposal aims to facilitate quadriceps strength and activation after ACLR via a novel training paradigm that incorporates operant conditioning of motor evoked responses of the quadriceps muscles. Traditionally, strength and activation deficits after ACLR are addressed using neuromuscular electrical stimulation and high-intensity progressive resistance training.[34,52-54] While these approaches induce marked adaptations in both the muscular and the nervous systems,[55] recovery is often suboptimal with most subjects showing > 30% of asymmetry between limbs at the time of discharge from rehabilitation. We believe that a key reason for this incomplete recovery is that traditional approaches do not *directly* address corticospinal dysfunction (e.g., reduced corticospinal excitability) after ACLR. This altered excitability of the corticospinal pathways reduces the neural drive to the quadriceps muscle thereby negatively affecting the force generating capacity of the quadriceps muscle. Thus, interventions aimed at restoring corticospinal function after ACLR is expected to successfully attenuate quadriceps activation deficits and improve quadriceps strength. Operant conditioning is a powerful method to enhance the functioning of the corticospinal pathways.[56-59] Indeed, in both animals and humans, appropriate conditioning of the corticospinal pathways has been shown to facilitate neural plasticity along with sustained improvements in motor functions.[57,59-61] While previous research has used the principles of operant conditioning to improve locomotor functions, our approach of operant conditioning of motor evoked responses to improve quadriceps strength and activation is unique and has not been explored before. Further, by conditioning the motor evoked responses, we will target the entire quadriceps muscle rather than a particular muscle. Finally, this project will also improve our current understanding of the role of corticalspinal reflex excitability in ACLR recovery process. Despite strong evidence indicating that cortical and spinal-reflex excitability are affected after ACL injury/surgery,[40,62,63] and are associated with quadriceps weakness and activation failure,[62,64] studies that evaluate the effects of modulating corticospinal function on quadriceps strength and activation are lacking. *This proposal will fill this important gap; thus, opening up new therapeutic possibilities of operant conditioning.*

STUDY DESIGN

This is a randomized, controlled pilot clinical trial to test the feasibility of operant conditioning to improve quadriceps strength and voluntary activation in patients who have undergone ACLR. Thirty-two participants will be randomly assigned to either 1) training group (operant conditioning) or 2) control group. Participants in the training group will practice to up-regulate their motor evoked responses. Participants in the control group will receive the exact same

protocol except they will not be trained to up-regulate their motor evoked responses. Quadriceps strength will be our primary outcome measure and voluntary activation will be our secondary outcome measure. Outcomes will be examined at ~5 study time points: 1) *Pre-intervention*: about 4-6 months after ACLR, 2) *During-intervention* (2 weeks, 4 weeks, and 6 weeks), and 3) *Post-intervention*: immediately after the 8-week intervention (Fig. 1).

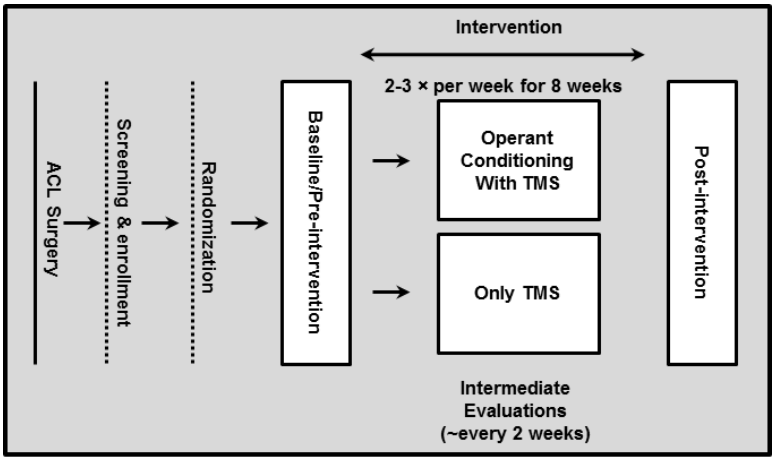


FIGURE 1. Schematic of the study Design

METHODS

Participants/Recruitment

We plan to recruit 32 patients who have suffered an acute ACL injury (e.g., suffered an ACL injury and have had an ACL reconstruction. We anticipate about 20 subjects (10 in each group) will complete all the evaluations. Recruitment will involve examining clinic schedules/medical records bi-weekly to identify potential participants, sending a member of the study team to describe the study and recruit the participant at their scheduled visit to MedSport. In our experience, it works best to approach patients after a physician has diagnosed their ACL tear or have scheduled/performed surgery and we will aim to recruit in this manner. At the clinic visit, we will gauge interest, send home the informed consent document with the patient (and parent/caregiver, if applicable) and follow-up with a phone call within a few days to confirm eligibility, willingness to participate, and schedule a time for their first testing session. The orthopedic surgeons at our institution perform well over 100 ACL surgeries and hence, we don't foresee recruitment issues. However, if recruitment is an issue, we will use flyers, newspaper advertisement, social media, etc. as additional methods of recruitment. We have used these methods in the past and have found them to be effective.

To be eligible for inclusion in the trial, patients must adhere to the following criteria:

Inclusion Criteria:

1) aged 18-45 years
2) suffered an acute, complete ACL rupture
3) scheduled to undergo/have undergone ACL reconstructive surgery
4) willingness to participate in testing and training sessions as outlined in the protocol

Exclusion criteria:

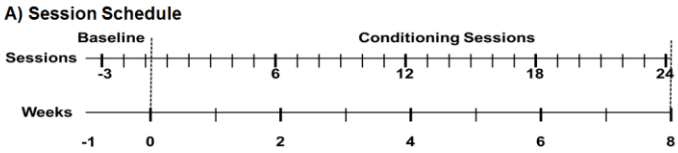
1) previous ACL injury to the contralateral knee
2) previous major surgery to the contralateral knee
3) history of recent significant knee injuries (other than ACL) or lower-extremity fracture
4) female subjects who are pregnant or are actively trying to conceive
5) history of uncontrolled diabetes or hypertension
6) any other major medical condition that will significantly impact the study results
7) subjects who are contraindicated for TMS (metal implants in head, cardiac pacemakers, cochlear implants, unexplained recurrent headaches, recent history of seizures, epileptogenic drugs, history of repeated fainting spells/syncope).

In order to promote the generalizability of our results to the population of interest (individuals with ACL ruptures), subjects with concomitant joint damage (defined as meniscal or ligamentous injury, subchondral bone contusions, and articular cartilage injury) will be included in the current study. Subchondral bone contusions are present in ~80% of patients, meniscal injury occurs in ~60% of patients, ligamentous injury (MCL, LCL, or PCL) in ~25% patients, and 14-46% of patients present with hyaline cartilage injuries.[65] While magnetic fields rapidly attenuate with distance and there are no known short-term or long-term risks of TMS to the children of pregnant women [66-68], we would still exclude individuals who are pregnant or are actively trying to conceive as there are no direct benefits to them from this study.

Interventions

Training Group (Operant Up-Conditioning of Corticospinal Responses)

Operant up-conditioning of motor evoked responses of the quadriceps muscle will be performed using custom-written evoked potential operant conditioning software according to the recommendations of Thompson et al.[58] Operant conditioning protocol will involve ~ 3 baseline sessions and up to 24 conditioning sessions (~ 3× per week for up to 8 weeks) (Fig. 2). Eight weeks was selected as that length is typically used in H-reflex and TMS operant conditioning paradigms.[57,69-72] Further, we have shown with previous interventions that changes in strength can be induced in healthy and ACLR subjects with exercises prescribed 2-3 x/week for 4-8 weeks.[34,73] In all sessions, quadriceps motor evoked torque and EMG responses will be measured while the subject is seated on a isokinetic dynamometer with their knees secured to the distal arm pad of the dynamometer. Motor evoked responses will be elicited using a Magstim 200 stimulator while the subject exerted a slight background contraction (~5% MVIC) of their quadriceps muscles. Recruitment curves of motor evoked potentials (MEPs) and evoked torque responses of the quadriceps muscle will be obtained over a range of TMS intensities (e.g., 70% to 140% AMT) at the beginning and end of each session. These procedures have been approved by UM IRBMED in prior applications (HUM00087962, HUM00081480, HUM00073356) During the baseline sessions, the recruitment curve will be followed by ~ three 75-trial blocks of control trials (~225 trials), in which the subject will receive TMS during slight background contraction. The subject will not receive any visual feedback on their evoked torque size or MEP and will not be asked to change their TMS-evoked responses. In each of the conditioning sessions, the TMS recruitment curve will be followed by ~20 control trials with procedures identical to those of baseline sessions. Following which, ~ three 75-trial blocks of conditioning trials will be performed. The conditioning trials will be identical to the control trials, except that the subject will be asked to increase (up-condition) the evoked torque response size and will be provided with immediate visual feedback as to whether torque size surpassed the criterion value (i.e., whether or not the trial was a success). The subject will be encouraged to maximize their training opportunity using established guidelines.[58] The reward criterion for the first block will be based on evoked responses from immediately preceding block of ~ 20 control trials, and the criterion values for the following block of conditioning trials will be based on the immediately preceding block of conditioning trials.[61,72] The subject will also be provided with a



B) Session Composition

Sessions	Protocol in Sequential Order
Baseline Sessions	TMS Recruitment Curve (70% to 140% AMT) ~225 Control Trials (~Three 75-trial blocks) TMS Recruitment Curve (70% to 140% AMT)
Conditioning Sessions	TMS Recruitment Curve (70% to 140% AMT) 20 Control Trials ~225 Conditioning/Training Trials (~Three 75-trial blocks) TMS Recruitment Curve (70% to 140% AMT)

Figure 2: Schematic of the session schedule and composition of operant conditioning protocol

modest monetary reward if the success rate exceeded 50% (20 cents for every percentage above 50%).[61] TMS intensity for the control and conditioning trials will be kept at approximately 10% above the active motor threshold (see below for procedures). All training sessions will be performed in the same fashion using standardized procedures and meticulous effort will be placed to ensure that the conditioning sessions are reproduced effectively during each training session, including the use of a camera system to assure consistent coil placements between sessions.

Control group training sessions

Participants in the control group will receive the exact same protocol mentioned above except they will not be trained to up-regulate their motor evoked responses.

ACL Standard of Care Rehabilitation

Participants in both groups (regardless of randomization assignment) will continue with their standard of care rehabilitation (if they are taking any) during the study period, as operant conditioning is being studied as an adjunct to the standard of care and is meant to supplement current practices.

Testing Measurements

Knee Strength and Voluntary Activation:
Quadriceps strength and voluntary activation will be measured with the interpolated triplet technique (ITT) as we have done previously.[15,74-77] Dr. Krishnan and his colleagues have more than 12 years of experience in performing these tests and have published extensively on this methodology. This methodology has been approved by the UM IRBMED in prior applications (HUM00080244, HUM00073356). This method provides detailed information about strength as well as the level to which a subject can activate the quadriceps muscle.[75,78-80] In this test, an electrical stimulus is introduced during a maximal voluntary isometric contraction (MVC) and during rest. When incomplete activation is present, the superimposed electrical stimulus augments the force/torque generated by the muscle. Conversely, when there is complete or nearly complete voluntary activation, there is little to no increase in force/torque when the electrical stimulus is introduced. Quadriceps strength symmetry index is then computed by normalizing peak torque of the reconstructed leg to that of the non-reconstructed leg. Voluntary activation is computed by comparing the voluntary torque at the time of stimulus delivery to the peak force/torque measured during superimposition of electrical pulses (as in Fig. 3). Intra- and Inter-session reliability for recording isometric quadriceps strength and voluntary activation are high (ICC range ≥ .92).[14,81-86]

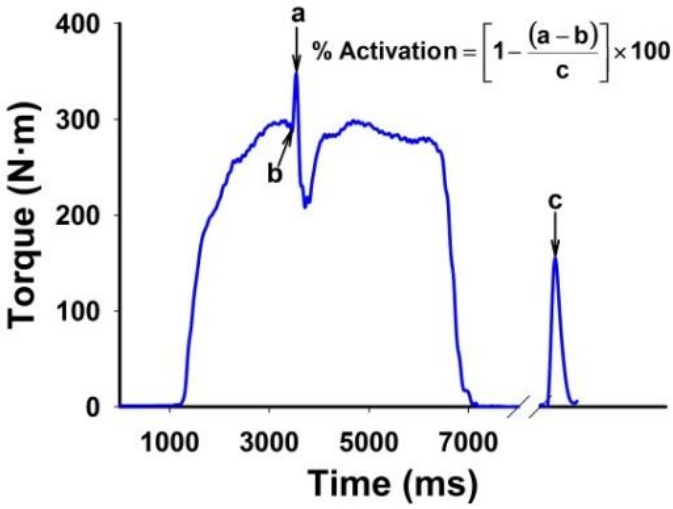


FIGURE 3 - Interpolated triplet technique.

Prior to testing, subjects will be provided with an opportunity to warm-up on a stationary bicycle. Following which, the skin over the electrode surface will be cleaned with alcohol swabs to minimize skin resistance and surface electromyographic (EMG) electrodes will be placed on the surface of the thigh and leg muscles according to the guidelines established by the international

SENIAM initiative (www.seniam.org). Subjects will be seated on an isokinetic dynamometer and will be secured to the system using chest, pelvis, thigh, and shin straps. The anterior thigh will be cleansed with alcohol and self-adhesive stimulation electrodes will be placed over the middle (cathode) and distal (anode) aspects of the quadriceps musculature. Subjects will be then be familiarized to the electrical pulses and subject-specific stimulus intensity will be determined for later use. This will be accomplished by stimulating the quadriceps muscle in current steps of ~100 mA until force plateaus using a constant current/voltage stimulator while the subject sits at rest. Current will then be reduced by 50 mA and a final stimulus will be provided. The current producing peak torque will be selected for use. In our experience, this approach ensures collection of quality data at the lowest possible stimulus intensity, thereby maximizing subject comfort.

Subjects will then perform a few sub-maximal (50%-75% of perceived effort) and one maximal isometric knee extension contractions to familiarize themselves with testing procedures performing isometric contractions in a manner that produces steady torque curves. Following a brief rest period, subjects will perform 3-5 MVCs of knee extension and flexion in an alternating manner. During contraction, a train of electrical stimuli at the stimulus intensity determined previously is introduced when the torque produced by the subject begins to diminish. A second stimulus of equal intensity is delivered shortly after the subject returns to rest in order to assess the muscle in its potentiated state. Brief rest periods (~1-2 minutes of rest) will be provided between each of the ITT trials. All strength and activation testing will be completed in both limbs. The mean and peak torque and activation values produced during testing will be used in the analyses.

Motor Cortical Excitability (MCE): MCE changes due to operant conditioning will be evaluated using reliable (ICC ≥ .82) single- and paired-pulse TMS protocols[87-90] similar to our prior studies.[74,91-96] Dr. Krishnan is a TMS expert and has more than 9 years of experience in TMS procedures. This methodology has been approved by the UM IRBMED in prior applications (HUM00087962, HUM00081480, HUM00073356) First, the optimal site for eliciting quadriceps motor evoked responses (i.e., hotspot) will be determined using a double cone TMS coil, which is specifically designed for stimulating the leg motor cortex.[97,98] The hotspot will be identified by determining the stimulation location that produces largest and most consistent motor evoked responses.[99-101] A custom designed coil tracking system will be used to assure consistent placement of the coil during the experiment.[102,103] Active motor threshold (AMT) will then be established during a slight background contraction (~5% MVIC) by finding the lowest stimulus intensity that elicits a clear and discernable motor evoked response in the majority of test stimulations. Recruitment curves will be created by measuring motor evoked responses of the quadriceps muscle over a range of TMS intensities (70% to 140% AMT). The intervention-mediated changes in cortical excitability will be assessed by examining the changes in MEP/torque amplitudes and slopes of recruitment curves obtained using Boltzmann equation.[104-107] In cases where sigmoidal relationship is not appropriate (R^2 < 0.80), other fits (e.g., linear) will be used as appropriate.[104] Intracortical excitability will be evaluated using a paired-pulse TMS paradigm.[90,108-110] Here, two TMS pulses (first pulse = conditioning pulse [<100% AMT]; second pulse = test pulse [>100% AMT]) will be applied through the same coil with an ISI between 1-30ms.[100,109,111] Conditioning pulse will decrease the amplitudes of TMS evoked torque and MEPs more than a single unconditioned pulse at the same intensity due to intracortical inhibitory mechanisms (short-interval intracortical inhibition). This inhibition is typically altered with changes in cortical excitability,[90] which will be quantified in each subject to determine their response to operant conditioning.

Survey Instruments

Demographic information to be recorded: The following demographic information will be recorded and reported for subjects participating in Aim 1 (as applicable):

- Age, height, weight, BMI, sex, and activity level
- ACL injury mechanism
- Date of injury, surgery, and time from injury to surgery
- Concomitant joint damage (determined during arthroscopy and from pre-surgical MRI)
- Treatment/repair of concomitant joint damage
- Joint laxity
- Activity Level (evaluated using the Tegner Scale and MARX Activity Scale)
- Pain and knee function (evaluated using IKDC, KOOS, Lysholm and PROMIS)

Tegner Activity Scale: The Tegner activity level scale is a scale that aims to provide a standardized method of grading work and sporting activities.[112] Scores on the Tegner can range from 0-10, with a score of 0 representing sick leave or disability pension because of knee problems and a score of 10 corresponding to participation in national and international elite competitive sports. This has been approved by the UM IRBMED in HUM00080244, HUM00110455.

MARX Activity Rating Scale: The MARX scale is an activity questionnaire designed to assess the activity levels and ability of participants to perform four tasks: running, cutting, deceleration and pivoting. The survey provides five different options for response to each of the tasks: less than one time a month, one time a month, one time in a week, 2 or 3 times a week, 4 or more times in a week. This scale's validity has been demonstrated in comparison to other survey's designed to assess activity levels. [113] This has been approved by the UM IRBMED in HUM00080244

International Knee Documentation Committee (IKDC) Form: Self-reported knee function will be quantified using the International Knee Documentation Committee (IKDC) subjective knee evaluation form. The form is scored on a scale of 0 to 100, with 100 representing highest knee function. The IKDC score has been shown to be a reliable and valid measure of function in persons with ACL injury.[114] This has been approved by the UM IRBMED in HUM00110455.

Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire: The KOOS questionnaire is a self-administered survey that assesses an individual's knee function across a spectrum of five domains: pain, symptoms, activities of daily living, sport and recreation function, and knee related quality of life.[38] Each question has five possible options: not at all, mildly, moderately, severely and totally. The KOOS score has been shown to be a reliable and valid measure of function in persons with ACL injury.[115] This has been approved by the UM IRBMED in HUM00080244.

Lysholm Knee Scoring Scale: The Lysholm Scale is a survey designed as a follow up measure to evaluate functional impairment in patient populations post knee ligament surgery.[116] The survey asks individuals to check the statement that best describes their current perceived experience with their knee in a post-surgical state. The statements cover eight main categories: limp, using cane or crutches, locking sensation in the knee, giving way sensation from the knee, pain, swelling, climbing stairs and squatting. The statements for participants to choose from vary between categories and are assigned points that when completed produce an additive score to gauge the degree of function of the knee post-surgery. This has been approved by the UM

IRBMED in HUM00080244.

Patient Reported Outcome Measurement Information System (PROMIS) Physical Function Questionnaire: The National Institutes of Health's (NIH) Patient Reported Outcomes Measurement Information System (PROMIS) is a national resource for precise and efficient measurement of patient-reported symptoms, functioning, and health-related quality of life, appropriate for patients with a wide variety of chronic diseases and conditions.[117,118] The PROMIS Physical Function questionnaire will be utilized in the current study and is aimed at assessing the subject's ability to stand and move with and without support.

STATISTICAL ANALYSIS

Descriptive statistics will be used to explore the distribution, central tendency, and variation of each measurement, with an emphasis on graphical methods. Normality for each variable will be checked using a Shapiro-Wilks test, and appropriate transformations (e.g., log) will be made when necessary. Repeated measures ANOVA with time as a within-subjects factor and group as a between-subject factor will be used to compare the changes in quadriceps strength and voluntary activation before and after the intervention. Pearson product-moment correlational analysis will be used to determine the association between changes in corticospinal excitability and changes in quadriceps strength and activation. The optimal length of intervention will be evaluated by examining the treatment-response curves generated using the baseline, intermediate, and post-treatment evaluations. Significant main or interaction effects will be followed by appropriate posthoc analysis with corrections for multiple comparisons (e.g., Bonferroni) when necessary. A significant level of $\alpha = 0.05$ will be used for all analysis.

BIOSTATISTICAL JUSTIFICATION

This is a pilot study and so sample size is based primarily on feasibility considerations. We provide the effect size that can be determined in the primary endpoint with sufficient (>80%) power with a two-sided type I error of 5%. We anticipate that about 20 subjects (~10 in each group) will complete the study. This sample size provides an effect size of 0.35 (partial η^2), a relatively large effect [G*Power 3.1.9.2]. Actual power may be greater or the magnitude of the treatment difference may be smaller, based on our analytic model which incorporates additional information. However, successful completion of this study will yield the estimates of variance and the magnitude of a clinically relevant effect size for planning future studies.

The number of subjects (N=32) to be consented for the proposed study includes subject dropouts and attrition after enrollment. The proposed sample size is also based on prior studies in healthy and neurologically impaired individuals.[57,61,72,119] These studies have demonstrated that significant conditioning effects can be observed with about 8-10 subjects in each group. Prior research using TMS conditioning protocols indicate that large effects (both in evoked responses and MVIC torque) can be observed in <10 subjects.[70,71] Since the basic study schedule of the current project is very similar to the ones used in those previous studies, we estimate that N=32 will be sufficient to obtain reliable preliminary results. Also, we believe that N=32 is a reasonable and feasible number of subjects to be studied with the proposed protocol and currently available resources.

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