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TITLE:Restoring Function After Volumetric Muscle Loss: Extracellular Matrix Allograft or Minced Muscle Autograft?

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14. ABSTRACT

We proposed a randomized surgical trial to restore muscle function following a severe muscle injury using muscle autograft intends to restore functional muscle units. The proposed surgical technique in this trial was a new surgical procedure using the patient's own autograft muscle tissue from a large, uninjured muscle group. Prior small and large animal studies in our laboratory have demonstrated that minced muscle autograft (MMA), by virtue of providing myogenic, angiogenic, neurogenic, and immune modulatory capacity to the injured area, results in regeneration of functional muscle units which integrate with underlying muscle mass. We hypothesized that minced muscle autograft (MMA) for the treatment of VML will yield greater restoration of muscle volume, greater improvement in validated functional measurements and self-reported outcomes, and greater myogenesis and single fiber strength compared to treatment with ECM. Despite multiple attempts at recruitment, potentially eligible subjects and potential subjects who were interested in undergoing additional surgery were unable to be identified. Once recruitment was determined to not be feasible, the trial was stopped early with no subjects enrolled.

15. SUBJECT TERMS: volumetric muscle loss, minced muscle autograft, extra-cellular matrix

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Introduction:

The extremities are the most commonly injured body site and the most common source of disability following combat injury. One sequela of extremity injury is the volumetric loss of skeletal muscle, resulting in a functional loss of muscle strength as well as a cosmetically challenging scar. We propose a randomized surgical trial to restore muscle function following a severe muscle injury. A new surgical procedure using muscle autograft may potentially which intends to restore functional muscle units which are both innervated and vascularized and which can contribute to both functional rehabilitation and cosmetic treatment of the muscle defect. This new surgical method will be compared to the only other currently available surgical option for volumetric muscle loss (VML), implantation of a porcine extra cellular matrix (ECM) scaffold, which has not conclusively been shown to be myogenic. The proposed surgical technique in this trial is a new surgical procedure using the patient's own autograft muscle tissue from a large, uninjured muscle group. The autograft muscle will be minced and placed intramuscularly at the site of the VML. Prior small and large animal studies in our laboratory have demonstrated that minced muscle autograft (MMA), by virtue of providing myogenic, angiogenic, neurogenic, and immune modulatory capacity to the injured area, results in regeneration of functional muscle units which integrate with underlying muscle mass without fibrotic scar formation, features not conclusively identified with prior study of ECM. We hypothesize that minced muscle autograft (MMA) for the treatment of VML will yield greater restoration of muscle volume, greater improvement in validated functional measurements and self-reported outcomes, and greater myogenesis and single fiber strength compared to treatment with ECM.

Keywords:

Volumetric muscle loss, minced muscle autograft, extra-cellular matrix allograft

Accomplishments:

What were the major goals of the project?
The original planned aims were as follows:

Specific Aim 1 Compare muscle form and function as determined by imaging and standardized rehabilitative outcomes measures compared to pre-operative measures between minced muscle autograft and extracellular matrix allograft
Major Task 1: Enroll 24 subjects for study participation
Major Task 2: Perform randomized test procedure
Major Task 3: Follow up evaluations

Specific Aim 2 Compare histologic muscle regeneration post operatively between minced muscle autograft and extracellular matrix allograft
Major Task 1: Obtain baseline biopsy for muscle characterization
Major Task 2: Obtain follow up biopsies for muscle characterization

What was accomplished under these goals?
The study protocol was submitted to the MRMC IRB in October 2016 and approved (including HRPO approval) 29 March 2017. The study PI conducted study training for the research personnel in April 2017. An amendment to add a shear wave ultrasound to measure muscle stiffness was approved on 05 July 2017. The use of the ultrasound allowed the study team to leverage resources already present at the ISR for muscle studies. A research assistant was hired for assisting with recruitment. A second amendment was submitted to add study personnel and allow for screening of upper extremity muscle loss as well as a potential way to improve enrollment.

Two control subjects were enrolled and provided control sample data. One potential subject who expressed interest was screened and found to be ineligible based on VML size and location. Multiple potential subjects were approached within the Department of Orthopaedics and at the Center for the Intrepid, though interest in the trial was low.

What opportunities for training and professional development has the project provided?
Not applicable

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?
Not applicable

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.

Changes/Problems

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
As noted in 2016 annual report, we encountered a significant delay in the project initiation. First, a large animal study at the ISR indicated some concerns with the extra cellular matrix (ECM) allograft that was going to be used in the trial. While there are human reports of this particular ECM being used without complication, the product caused wound complications in the porcine model. This prompted us to pause protocol development until another proprietary ECM was tested in this model. This delay was reported at the study IPR in February 2016 at Ft. Detrick, MD. Once the additional porcine study was completed without wound complication, the protocol writing resumed resulting in the protocol submission in March 2016 to the ISR RRCD office. ISR RRCD office submitted the protocol for the MRMC IRB review in October 2016. We did not receive approval until 29MAR2017. The ECM selection and the regulatory timeline has caused a significant delay in protocol initiation.

Once the study started, multiple attempts at recruitment were made by the PI and study staff. Flyers were distributed and the Department's surgeons were educated on how to refer subjects to the research staff if encountered. Potential subjects with VML who were presented with the trial were not interested.

As the non-feasibility of the recruitment was realized, the trial was stopped with no subjects enrolled.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report.

Products:

Publications, conference papers, and presentations
Nothing to report.

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: Jessica Rivera
Project Role: PI
Nearest person month worked: 0.60
Contribution to Project: Dr. Rivera serves as the study PI on this research project. MAJ Rivera provided the necessary programmatic leadership, administrative oversight and support for all aspects of the proposed work to be conducted in accordance to human subjects research protections, ensuring that personnel and departmental resources are properly aligned to achieve the goals of this study. She met with the key personnel on a regular basis to review planning and execution of the proposed project. Finally MAJ Rivera was responsible for the preparation of technical reports, manuscripts, and other dissemination materials generated by this study.

Name: Joshua Mercer
Project Role: Research Assistant
Nearest person month worked: 12
Contribution to Project: Mr. Mercer took on major recruitment efforts by attending orthopaedic and CFI clinics, working closely with surgeons who may see the pertinent patient population and worked closely with Dr. Rivera to review goals and objectives for the protocol. He assisted in preparation of protocol closure submission to the IRB.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report. MAJ Rivera separated from the military after the early closure of the trial.

What other organizations were involved as partners?
Nothing to report.

Special Reporting Requirements

Nothing to report.

"Restoring Function after Volumetric Muscle Loss: Extracellular Matrix Allograft or Minced Muscle Autograft?"

Log Number: OR140269

Award Number: W81XWH-15-2-0086

PI: Dr. Jessica Rivera **Org:** The Geneva Foundation/United States Army Institute of Surgical Research **Award Amount:** $1,102,796.00

Study/Product Aim(s)

- Compare muscle form and function as determined by imaging and standardized rehabilitative outcomes measures compared to pre-operative measures between minced muscle autograft and extracellular matrix allograft
- Compare histologic muscle regeneration post operatively between minced muscle autograft and extracellular matrix allograft

Approach

This study is a randomized pilot of a new surgical technique to treat volumetric muscle loss using mince muscle autograft compared to the only other tested muscle repair procedure using an extracellular matrix allograft. Subjects with small VMLs of the leg who have a functional deficit will be enrolled and randomized to on or the other surgery. Study evaluations post op will include functional measurements and muscle histology.

Accomplishment: Protocol approved and amendment submitted and approved. Study team in place and new assistant identified to start August 2017 to focus on enrollment. One subject screened and found to be ineligible. Two controls enrolled.

Timeline and Cost - POP: 30 Sep 2015 - 29 Sep 2018

Activities CY	15	16	17	18
IRB approval/initiate recruitment				
Subject recruitment/ enrollment				
Continue evaluations				
Complete evaluations and analysis, data dissemination				
Estimated Budget ($1,102,796)	**86.1k**	**362k**	**396.9k**	**257.7k**

Updated: 29 Sep 2018

Goals/Milestones

CY16 Goals – Enrollment

DELAYED until CY17

CY17 Goal – Enrollment, Follow ups

■ Subject recruitment begins

☐ Initial enrollees undergo surgeries

☐ Ongoing enrollment/surgeries

☐ Continue and complete follow ups on initial enrollees

CY18 Goal – Complete Follow ups, Analysis

☐ Continue and complete follow ups on remaining enrollees

☐ Analysis of data and dissemination

Comments/Challenges/Issues/Concerns

- Regulatory issues (now resolved) delayed initiation

Budget Expenditure to Date

Total Projected Expenditure: $1.1M

Actual Expenditure: $175K