Clinical Trial Research Study Protocol

Date: October 23, 2020

Official Protocol Title:

A Prospective Double Blinded Randomized Controlled Trial Examining the Effectiveness of a Connective Tissue Matrix Implant in Reducing Post-operative Pain and Narcotic Use in Patients Under 55yo After Outpatient Rotator Cuff Surgery

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Introduction

This document is a protocol for a human research study. This study is to be conducted according to United States standards of Good Clinical Practice in accordance with applicable Federal regulations and institutional research policies and procedures.

Extracellular matrix grafts have been used to help with postoperative inflammation

Background Information and Scientific Rationale

Shoulder surgery has evolved over the past decade with many procedures now done on an outpatient basis. Multimodal pain management strategies and regional anesthesia have greatly contributed to this transition and newer strategies continue to evolve. Uncontrolled pain can often lead to readmissions, prolonged hospital or ambulatory stays and an overall negative patient experience. Despite improvements in regional anesthetic technique and newer longer acting medicines such as liposomal bupivacaine, the duration of pain relief is often only over the course of 72 hours postoperatively. Post-operative pain beyond 72 hours is largely inflammatory in nature. As such, biologic approaches to reduce surgical tissue damage-induced inflammation is an attractive therapeutic addition to surgical procedures. These approaches are especially relevant in light of the current opioid epidemic plaguing the United States.

Flowable, placental-derived connective tissue matrix (pECM) is a potential option to supplement damaged tissue prone to inflammation as it introduces nascent, hydrated components of the inflammatory phase, including structural proteins and growth factors, which allow for efficient repair. Derived from relatively immune-privileged tissue, placental-derived pECM elicits little or no immune response in recipients. They have been shown to greatly reduce inflammatory cell influx and inflammatory cytokines present in dermal and mucosal surgical sites post-operatively. Moreover, placental-derived pECM reduces expression of prostaglandin E2, a potent pain mediator, *in vitro*. In the orthopedic space, ECM has been used effectively to reduce pain following spinal fusion and for treatment of knee arthritis. Taken together, biologic therapies directed at modulating inflammation and associated pain is an increasing area of interest with far reaching implications.

The purpose of the current study is to prospectively analyze two groups of patients treated for rotator cuff repair with and without a flowable pECM to determine if a significant reduction in pain and opioid consumption as measured in morphine equivalent units is demonstrated within the first 6 weeks of surgery. Furthermore, patients will be compared in regard to early range of motion and patient reported outcomes to determine if a difference is present when the ECM is utilized within the first 6 months of surgery. This is the first double blinded prospective series in the shoulder literature to date looking at a pECM graft for pain reduction and improved range of motion perioperatively.

Study Objectives

Utilizing a prospective randomized controlled trial, the aim of this study is to assess modulation of post-operative pain and narcotic use when a placental-derived extracellular matrix is injected into the bed of the repair following outpatient rotator cuff repair surgery. Furthermore, this study aims to determine if the addition of pECM influences patient reported outcomes and influences early postoperative range of motion.

Primary Aims & Objective

Aim 1a: To assess post-operative narcotic consumption (measured in morphine equivalent units) between patients treated with flowable placental-derived pECM compared to those patients undergoing rotator cuff surgery.

Hypothesis: Narcotic consumption (measured in morphine equivalent units) will be reduced in patients treated with an extracullar matrix graft as compared to those patients undergoing rotator cuff surgery without.

Objective: Utilizing a prospective randomized controlled trial, narcotic use will be measured for 12-hour increments for a total of 7 post-operative days (PODs) then once on POD 14, 21, 28, and 42. . Consumption will be measured by the number of tablets ingested and converted to morphine equivalent units and compared between the two treatment groups.

Aim 1b: To determine if flowable placental-derived pECM decreases patient-reported post-operative VAS pain in patients undergoing outpatient rotator cuff surgery

Hypothesis: There will be a decrease in VAS pain for up to 6 weeks post-operatively among participants who receive pECM, as compared to the control group (no pECM).

Objective: Utilizing a prospective randomized controlled trial, post-operative patient-reported VAS pain (on a scale of 0-10) will be collected 2 times per day (every 12 hours) for 7 post-operative days (PODs); then an average score collected on POD 14, POD 21, POD 28, and POD 42. Scores will be averaged and compared between the two treatment groups for the first 7 days, 2 week, 3rd week, 4th week and 6th week postoperatively.

Secondary Aims & Objectives

Aim 2a: To assess patient-reported outcomes and early range of motion (measured in morphine equivalents) in patients treated with flowable placental-derived pECM compared to patients injected with saline control.

Hypothesis: There will be improved patient reported outcomes and early range of motion measured at 6 weeks and 3 months and 6 months postoperatively in patients receiving and extracellular matrix injection following outpatient rotator cuff surgery.

Objective: Utilizing a prospective randomized controlled trial, patient reported outcomes as measured by American Shoulder and Elbow Score, Simple Shoulder Test and SANE scores and range of motion (External rotation, internal rotation and forward flexion) will be collected preoperatively and at 2 weeks (external rotation), 6 weeks (all)) , 3 months (all) and 6 months (all) postoperatively. Scores and range of motion measurements will be averaged and compared for differences between the two groups.

Study Design

The study design is a randomized double-blind randomized controlled trial.

Research Design

Patients will be randomly assigned to one of two treatment groups (see Intervention Description). Patients will randomly select one of 70 sealed envelopes the day of surgery. Patients will be blinded to the medication utilized as well as the treating surgeon (PI). A consecutive series of patients will be enrolled to prevent selection bias. A single surgeon will be performing all procedures to minimize variability. Upon completion of the surgery, a spinal needle will be loaded into the substance of the rotator cuff tendon under direct arthroscopic visualization. The surgeon will then leave the room and the envelope will be opened by the circulating operating room nurse. If the patient is in the treatment group, 2cc of an extracellular matrix graft be opened and then injected with a 22g spinal needle already placed into the bed of the repair by the physician assistant. Those patients that are in the control group will have the needle removed and no injection administered. The envelope will be then sealed with the patient's name and treatment group to allow for data analysis upon completion of the study.

Data Collection will occur post-operatively for 6 months. Data will be collected at 20 timepoints, in total for pain and opioid consumption. For the first seven days, data will be collected at 12-hour time intervals beginning the first evening of the surgery (POD0) at 8pm then at 12-hour intervals for the next 7 days (POD7). Data will be collected using PatientIQ, an application that uses text message or email to collect information. The day of surgery (POD0) the first text will occur at 8pm. Patients will then be notified by text alert 2 times per day (8am and 8pm) asking to rate their pain on a scale of 0-10 (VAS) beginning on POD 1 thru POD 7. Patients will also respond to the number of pain pills taken in the slotted time span. All patients will be prescribed the same narcotic regimen (oxycodone IR) barring any allergies encountered. Patients who fail to respond to the text alert will be notified by the data collection system and contacted via phone by study personnel. Patients lacking smartphone technology will all be notified via telephone and also asked to keep a personal log to capture the information needed.

Data Management

Patient IQ is password protected and HIPPA compliant data collection system. Patients upon enrollment will be assigned an ID to allow for data tracking within the application. The application does not have access to other personal information on the patient's electronic device. Primary data will be collected via the web-based system and stored electronically and encrypted under password protection. The principal investigator will only have access to the database. At the conclusion of the study, the data will be exported to a password-protected encrypted Excel file on a password-protected computer. Once the data have been checked for accuracy and prior to statistical analysis, patient identifiers will be removed from the data set. The de-identified password-protected Excel spreadsheet will be provided to a statistician who will import the file into SPSS for analysis.

Study Agent, Device, and/or Intervention Description

The pECM graft administered at completion of the surgery is the intervention in this study. Study participants will be randomized into one of two groups. The treatment groups are listed below:

Group 1 (Control)	Group 2
Standard rotator cuff repair and no pECM injection	Rotator cuff repair and 2cc of pECM injection into perimeter of repair

Sample Size

For an analysis of variance (ANOVA) test, a sample size of 28 participants per group would be required, given an effect size of f=0.30 a power of 80%, and a two-tailed alpha level of 0.05. However, to account for 20% subject attrition, a total of 35 patients per group will be enrolled, yielding a total of 70 participants.

Subject Selection

Patients who meet the following criteria will be included in the study:

Inclusion Criteria

1. Age 18 and older
2. Primary diagnosis of rotator cuff tear
3. Able to provide informed consent
4. Is willing and able to accept text messages

Patients who meet the following conditions will be excluded from participation:

Exclusion Criteria

1. Older than 55 years old.
2. Pregnancy.
3. Known narcotic or alcohol abuse (< 3 months)
4. Revision rotator cuff surgery
5. Current narcotic regimen or contract with pain management specialist

Study Outcome Measures (Endpoints)

Primary Endpoint: Patient-reported post-operative VAS pain (on a scale of 0-10), measured post operatively, in 12-hour increments, for a total of 7 days postoperatively and then once per day on POD 14, 21, 28 and 42.

Patients will be prompted via text message to provide VAS pain every 12 hours for the first 7 days and then once per day at later timepoints. If a response text message is not received, a phone call will be made to obtain the information. Patients who do not have a smart phone will receive a phone call or keep a personal log of VAS pain.

Secondary Endpoint: Patient-reported post-operative opioid use (converted to morphine equivalents), collected post operatively, in 12-hour increments for the first 7 days and then once per day on POD 14, 21, 28 and 42.

Patients will be prompted via text message to provide the amount of narcotics (number of pills converted to morphine equivalents) taken over the course of the previous 12 hours. If a response text message is not received, a phone call will be made to obtain the information. Patients who do not have a smart phone will receive a phone call or keep a personal log of narcotic use.

Study Procedures

Subject Recruitment and Screening

Participants will be recruited from the clinical practice of Dr. Brian Badman. Patients who present for an office visit and are diagnosed with a rotator cuff tear requiring outpatient surgical intervention will screened for eligibility for participation in the study. If a patient is eligible for the study, Dr. Badman will discuss the study with the patient and obtain informed consent during the routine office visit.

Randomization

This is a double-blinded study, thus, neither the surgeon nor the patient will know if a pECM injection is used. A total of 70 envelopes will be generated consisting of 35 with Group 1" (no pECM) and 35 with "Group 2" (pECM Injection). Envelopes will be sealed and randomly chosen prior to surgery. Once the envelope is opened to determine if pECM is to be injected, the name of the patient will be added to the envelope along with the treatment group, and the envelope will be sealed. The treatment group and name of patient will be kept confidential until completion of the study. Envelopes will be opened at end of study for data collection and analysis purposes with patient information deidentified. They will be stored in a locked container at the surgery center only accessible by the chief of staff. Patients will be blinded to the treatment as well as the treating surgeon. The physician assistant will not be blinded as she will administer the injection for the treatment group but will keep the information confidential. She will not participate in follow-up data collection of the patients in this study postoperatively.

Study Visits/ Study Duration

Participants enrolled in this study will be followed for a period of 6 months post-operatively. For the first week, twice per day (12-hour increments), patients will self-report VAS pain and indicate their narcotic use (number of tablets ingested). Data concerning pain and narcotic use will be collected via text message (or phone if patients fail to respond to text messages).

Post-operative day (POD)	Data Collection Time	Data to be Collected
POD 0	8PM	VAS; #pain pills used
POD1	8AM	VAS; #pain pills used
	8PM	VAS; #pain pills used
POD2	8AM	VAS; # pain pills used
	8PM	VAS; # pain pills used
POD3	8AM	VAS; # pain pills used
	8PM	VAS; # pain pills used
POD4	8AM	VAS; # pain pills used
	8PM	VAS; # pain pills used
POD5	8AM	VAS; # pain pills used
	8PM	VAS; # pain pills used
POD6	8AM	VAS; # pain pills used
	8PM	VAS; # pain pills used

POD7	8AM	VAS; # pain pills used
	8PM	VAS; # pain pills used
POD14 (2 weeks)	Office Exam	ER (neutral); ASES; SANE; SST
	8PM	VAS; # pain pills used
POD21 (3 weeks)	8PM	VAS; # pain pills used
POD28 (4 weeks)	8PM	VAS; # pain pills used
POD42 (6 weeks)	Office Exam	ER (neutral and scapular/IR-scapular/FF; ASES; SANE; SST
	8PM	VAS; # pain pills used
3 months	Office Exam	VAS; ER (neutral and scapular/IR-scapular/FF; ASES; SANE; SST
6 months	Office Exam	VAS; ER (neutral and scapular/IR-scapular/FF; ASES; SANE; SST

The enrollment period for study participation is anticipated to last for 12 months only for data analysis.

Specimen Collection, Preparation, Handling and Shipping

N/A

Statistical Analysis Plan

After data checking and validation are completed, the analysis of the data will begin with examination of the distribution of each of the study variables. In this process, outliers will be identified and evaluated for inclusion in the final study database. Appropriate summary statistics will be calculated. Means and standard deviations will be reported for normally distributed continuous variables, a median and range will be tabulated for continuous variable that are not normally distributed, and frequencies and percentages will be provided for categorical variables. The remainder of the analysis will correspond to the specific aims provided above.

Specific Aims 1a-b:

To determine if there is a difference in patient-reported post-operative narcotic use (measured in morphine equivalents) among two groups.

If data are normally distributed, analysis of variance (ANOVA) with Tukey's HSD pairwise comparisons will be used to compare narcotic use (converted to morphine equivalents) between the three groups at each PODs. Cumulative narcotic use during all PODs will also be compared between groups. If data are not normally distributed, then Kruskal-Wallis with Dunn's multiple comparisons tests will be used.

To determine if there is a difference in mean VAS pain between the control group and ECM group postoperatively.

If data are normally distributed, analysis of variance (ANOVA) with Tukey's HSD pairwise comparisons will be used to compare VAS pain between the two groups at each PODs 1-7, 14, 21, 28 and 42. If data are not normally distributed, then Kruskal-Wallis with Dunn's multiple comparisons tests will be used.

Specific Aim 2:

To determine if there is a difference in clinical and functional outcomes of patients with rotator cuff tears treated with the nanofiber scaffold compared to those treated without.

If data are normally distributed, independent t-tests will be used to compare VAS Pain, SANE, V-12, ASES, and ROM measures between the control and intervention groups at each preoperative and postoperative timepoint. If data are not normally distributed, then Mann-Whitney U tests will be performed.

Potential Risks and Benefits

Potential Risks

This research is collecting data on human tissue implants which are routinely used in surgical repair. They are all FDA registered. The following risks can be related to the procedure, study analysis, and medications given:

1. Risk of extracellular matrix injection: Like any medical procedure, there are risks associated with the procedure itself. Theoretical risks associated with the extracellular matrix injection include infection, allergic reaction and injection site irritability. These risks are inherently low risks associated with administration.

2. Risk of text alerts: A HIPPA compliant and password protected database called Patient IQ is the application that will help gather and collect the data. Texting is not a secure form of communication and there is a risk of loss of privacy by entering the data. Measures to lessen these risks include using a password protected database and all personal information will be deidentified with your name removed. In addition, the only information you will provide will be regarding pain level and number of pain pills taken. Your phone number will be kept confidential and not shared with any outside party.

Potential Benefits

An individual benefit from this study is that patients will be monitored closely via text messages two times per day; thus, if any side effects or complications occur related to the injection, the PI will be alerted. Additionally, knowledge gained from this study will allow investigators to determine the most effective treatment methods for minimizing post-operative pain and narcotic use in patients who undergo outpatient rotator cuff surgery. These findings will benefit future patients.

Adverse Event Reporting:

Adverse Events

Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately. All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document.

Notification of Adverse Events

All adverse events will be reported according to WIRB guidelines.

Ethical Considerations

N/A

Funding Source

N/A

Subject Stipends or Payments

N/A

Publication Plan

The paper will be submitted for publication in the Journal of Shoulder and Elbow Surgery or the Journal of Bone and Joint Surgery upon completion.

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