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Title: Ability of Oral Steroid (Oxandrolone) to Halt Fatty Infiltration and Aid Rotator Cuff Healing: A Double-Blind, Randomized Clinical Trial

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1.0 Background

Rotator cuff tears are currently one of the most common causes of musculoskeletal pain and disability, and affect between 30% and 50% of the adult population over the age of 50 years.^{16,17} A torn rotator cuff can cause progressive loss of shoulder function and significant pain.^{4,5} The ramifications of rotator cuff tears are realized at both the individual and societal level where the direct costs of diagnosis and treatment and the indirect costs of loss of income, missed workdays, and disability payments continue to rise at exponential rates.^{17,18} The rate at which arthroscopic rotator cuff repair is being performed has increased by greater than 500% over the last 15 years.^{18,19} Given these high personal and societal costs, it is paramount to improve rotator cuff healing rates and decrease re-tearing and the need for reoperation.

Significant advancements in arthroscopic surgical techniques have led to a more stable mechanical environment to promote rotator cuff healing following repair.²⁰ Despite these major technical advances, there has been relatively slow progress consistently improving the biologic environment of healing tissues. This is especially true for rotator cuff repair where incomplete healing and re-tears remain a common postoperative complication. Studies suggest re-tear rates of up to 40% following small and medium tear repairs, and as high as 94% following for large and chronic tear repairs.^{21,22} Failure to heal the rotator cuff and rotator cuff re-tearing have clinical ramifications aside from the aforementioned societal and financial implications. Longitudinal clinical studies have demonstrated decreased functional improvement, diminished clinical outcomes, and lower patient satisfaction in those that have failure of healing or re-tears following rotator cuff repair.^{4,5}

There are many predisposing factors that may prompt rotator cuff healing failure or re-tear. These factors can be divided into patient-specific factors (patient age, gender, body-mass index (BMI), smoking status, and comorbidities) and tear-specific factors (tear pattern, tear size, and tear chronicity).^{23,24} The major biologic sequelae of a constellation of both patient- and tear-specific factors are the changes to the muscle-tendon unit.^{7,25} The hallmarks of these changes are muscle atrophy, fatty infiltration, and intercellular fibrosis of the torn rotator cuff muscle-tendon unit.^{7,25} These changes begin at the time of the tear and currently go largely unaddressed at the time of repair.

Researchers have pursued biologic augmentation at the time of arthroscopic rotator cuff repair; however, time-zero modifications to the healing interface with growth factors, platelet-rich plasma, and stem cells have failed to address the hallmarks of the biologic problem (muscle atrophy, fatty infiltration, and intercellular fibrosis).²⁶ Therefore, these modalities in both preclinical and clinical models have failed to consistently demonstrate improvements in healing rates, re-tear rates, functional results, or patient satisfaction.²⁷⁻²⁹ Recently, researchers have attempted to address the biologic hallmarks of rotator cuff tearing with a series of animal studies examining the effects of anabolic steroids on rotator cuff healing.^{25,30,31} This line of preclinical studies demonstrated that anabolic steroids, when administered as an adjuvant to rotator cuff repair, can halt the progression of fatty infiltration, decrease muscle atrophy, and promote rotator cuff healing.

Despite the wide range of doses in controlled clinical trials, our proposed dose has not been studied. The drug manufacturer, Gemini Labs LLC, is providing the drug in 6mg doses for the study and the proposed oxandrolone dose in men is 24mg/day. Currently, the FDA-approved dose in adults is up to 20mg/day, usually in two to four divided doses. Most controlled studies use doses of 5–20mg/day.^{3,36} In patients with moderate to severe alcoholic hepatitis, however, doses have been given up to 80mg/day.³⁷ Adverse events are typically dose-dependent and correlate to the duration of use.³⁶ Serious hepatic toxicity has not been shown with short term (≤ 3 months) treatment of oxandrolone, even with up to 80mg/day.^{36,37}

The objective of this research proposal is to perform a clinical trial, translating this previous line of preclinical research into the clinical arena. The purpose of this double-blind, randomized study is to compare the outcomes of rotator cuff repair augmented with 12 weeks of an oral, FDA-approved anabolic steroid to the outcomes of rotator cuff repair augmented with 12 weeks of placebo medication. The long-term implications of this study has the potential to provide direct and immediate clinical impact and healthcare savings by aiding rotator cuff healing.

2.0 Objectives and Purpose

Specific Aim #1. Determine if oral Oxandrolone administration will improve rotator cuff healing following rotator cuff repair.

Oxandrolone is an orally administered synthetic derivative of testosterone that is approved by the Federal Drug Administration (FDA) in patients who have lost weight resulting from extensive surgery, severe trauma, chronic infection, or as an adjunctive therapy to promote weight gain. It is also approved for bone pain associated with osteoporosis, and to attenuate protein catabolism associated with the prolonged use of corticosteroids. Oral administration of Oxandrolone has demonstrated increases in lean mass, protein synthesis, and wound healing with no long-term adverse events in trauma patients as well as healthy male controls.¹⁻³ The aforementioned safety and efficacy profile of oral Oxandrolone makes it an appealing adjuvant treatment to counteract the major biologic consequences of a chronically torn rotator cuff (muscle atrophy, fatty infiltration, and intercellular fibrosis), which are known to lead to poor healing and diminished clinical outcomes.^{4,5} The primary aim of this double-blind, randomized study is to compare the rotator cuff healing rates between an experimental group receiving 12 weeks of daily, orally administered Oxandrolone following rotator cuff repair to a control group undergoing the same rotator cuff repair and receiving 12 weeks of a daily, orally administered placebo medication. The healing spectrum from complete healing to re-tear will be defined based on a previously validated diagnostic imaging metric. The primary outcome measure is rotator cuff muscle-tendon structural healing as measured by the Sugaya classification on magnetic resonance imaging (MRI) at the primary end-point of 6 months.⁶ We will continue to follow for one year. We hypothesize that those in the experimental group (Oxandrolone group) will have greater rotator cuff tendon structural healing as compared to the control (Placebo group) at the primary end-point of 6 months post-operative.

The secondary measure of healing will be the degree of fatty infiltration of the muscle-tendon unit on MRI using the Goutallier grading classification.⁷ We hypothesize that those in the experimental group (Oxandrolone group) will have less fatty infiltrate as compared to the control (Placebo group) at primary end-point of 1 year.

Specific Aim #2. To determine if oral Oxandrolone administration will improve shoulder functional outcomes following rotator cuff repair.

Multiple rotator cuff repair studies have demonstrated that patients with MRI evidence of rotator cuff muscle-tendon healing following repair have improved function in the form of postoperative range of motion and strength.^{8,9} The secondary aim of this double-blind, randomized study is to compare the functional outcomes between the experimental group (rotator cuff repair and 12 weeks of Oxandrolone) and the control group (rotator cuff repair and 12 weeks of placebo). Functional outcome will be defined based on the literature standards of postoperative shoulder active range of motion and isometric strength.^{10,11} We hypothesize that those in the experimental group will have improved shoulder functional outcomes following rotator cuff repair compared to the placebo group at 1 year. .

Specific Aim #3: To determine if Oxandrolone administration will improve patient-reported outcomes (PROs) and patient satisfaction following rotator cuff repair.

Rotator cuff muscle-tendon healing following repair is also associated with improved patient-reported outcomes (PROs) and patient satisfaction.^{8,9} The third aim of this double-blind, randomized study is to compare the PROs and satisfaction level between the experimental group (rotator cuff repair and 12 weeks of Oxandrolone) and the control group (rotator cuff repair and 12 weeks of placebo). Patient-reported outcome will be defined based on the validated American Shoulder and Elbow Surgeons Shoulder Assessment (ASES) and a Visual Analog Pain Scale (VAS).¹¹⁻¹³ Patient satisfaction will be assessed with the literature standard, single-stem patient acceptable symptom state (PASS)

questionnaire.^{11,14,15} We hypothesize that the experimental group will have improved patient-reported outcomes and satisfaction compared to the placebo group at 1 year.

3.0 Study Design

Trial Design

This is a single-center, prospective 1:1 double blind randomized control trial. The trial will be conducted at the University of Southern California (USC), Keck School of Medicine in Los Angeles, California. Patients will be recruited from the Department of Orthopaedics. Men and women, 40–75 years of age, with MRI proven rotator cuff tears, indicated and scheduled for repair will be eligible for inclusion. Men and women with acute tears and those with significant comorbid liver, lung, cardiac, and kidney conditions will be excluded. Women who are pregnant or nursing will also be excluded. Women of child-bearing potential will be required to take a monthly urine pregnancy test and be on an agreed upon contraceptive. Participants will be randomized into one of two groups, a control group (receiving placebo medication) and an experimental group (receiving oral Oxandrolone, 12 mg twice daily for men and 6 mg twice daily for women for 12 weeks). Dosing will begin at the time of surgery and continue for 12 weeks, with medication dispensed by the USC Pharmacy. The study will be double-blinded: neither the treating surgeon nor the patient will know to which group the patient is enrolled.

Surgical Procedure

Arthroscopic inspection of the shoulder will be performed to verify the presence of a rotator cuff tear and to measure the size of the tear. In all cases a standard arthroscopic double-row technique will be used to repair the rotator cuff tendon.^{19,20} Treatment of the biceps tendon, need for subacromial decompression, and/or acromioclavicular joint resection will be at each surgeon's discretion. Intraoperative measurements of rotator cuff tear type and size as well as the details of the surgical procedure will be recorded.

Postoperative Rehabilitation

All participants in the study will undergo a standardized rehabilitation protocol for rotator cuff repair as agreed upon by the surgeons involved. Rehabilitation will be supervised by a licensed physical therapist. Adherence to the rehabilitation protocol will be assessed by review of patient treatment logs. If there are alterations to the standard postoperative rehabilitation course, the treating surgeon will be notified and will determine if the alteration in course warrants removal from the study. Patients who do not meet 80% adherence to the standardized protocol will be considered non-compliant and controlled for in the data analysis.

Feasibility

The study team has the experience, knowledge, and capability to conduct this study. The surgeons involved perform approximately 400 rotator cuff repairs per year. The study team assembled has conducted similar prospective studies in the past on rotator cuff healing. In addition, the study team has experience with clinical trials involving anabolic steroids.

The collaborative nature of the study is exemplified in the sharing of responsibilities. The majority of the clinical care proposed in this study (demographic data, medical history, physical examinations, vital signs, preoperative MRI without contrast) is standard-of-care treatment for rotator cuff tears all surgeons involved and will be overseen as such. The outcome measures collection will be monitored by a research coordinator through the Department of Orthopaedic Surgery. The research coordinator will be responsible for arranging follow-up care and confirming that postoperative MRI, functional tests, and patient-reported outcome measure are completed. The safety profile including laboratory tests and body composition will be performed under the guidance and monitoring of Dr. Schroeder based on his extensive knowledge of the anabolic steroid field. The body composition measurements will be made in Dr. Schroeder's

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laboratory. Postoperative rotator cuff repair rehabilitation and patient-reported outcome data will be overseen by Dr. Michener, given her career-long expertise in shoulder-specific rehabilitation and shoulder pathology patient-reported outcome measures. In addition, patient recruitment will not be an issue as the study-eligible population significantly overlaps with the patient population most frequently affected by symptomatic, chronic rotator cuff tears.

Key Personnel

George F. “Rick” Hatch III, MD is an assistant professor in the Department of Orthopaedic Surgery at the Keck School of Medicine of USC and the director of the USC Orthopaedic Surgery Sports Medicine Fellowship. He specializes in sports medicine, with a focus on disorders and injuries affecting the shoulder, elbow, and knee. His research interests focus on shoulder instability, stability of the reverse total shoulder prosthesis, treatment of infected shoulder prosthesis, outcomes following multi-ligament knee injuries and testosterone supplementation in orthopaedic post-operative rehabilitation. Dr. Hatch is a member of multiple orthopaedic societies including: The American Association of Orthopaedic Surgeons, The American Orthopaedic Society of Sports Medicine, The Western Orthopaedic Association, and The Arthroscopic Association of North America. In addition, Dr. Hatch is an elected member of the American Shoulder and Elbow Surgeons, the most exclusive and prestigious specialty society in the United States for shoulder and elbow surgeons.

Alexander Weber, MD is a specialist in the field of orthopaedic surgery and sports medicine at USC. Dr. Weber’s practice has an emphasis on arthroscopic surgery of the shoulder, elbow, hip, and knee. He also has specialized training in all types of shoulder replacement. He has research and clinical interests in the treatment of the athlete’s hip and biologic solutions to cartilage restoration. He has lectured nationally and internationally on hip arthroscopy for the treatment of FAI and cartilage preservation/restoration of the knee and has authored scientific articles and book chapters that advance the clinical practice of Orthopaedics and sports medicine.

E. Todd Schroeder, PhD is the director of the Clinical Exercise Research Center at the University of Southern California, Division of Biokinesiology and Physical Therapy and has conducted numerous clinical investigations with androgens including oxandrolone.

Anthony Essilfie, MD is a 3rd year orthopaedic surgery resident at LAC+USC medical center. He has particular interest in arthroscopy of the shoulder. He will be assisting with coordination of the study and cooperation with the IRB.

K. Soraya Heidari, BA is a fourth year medical interested in pursuing a career in orthopaedic surgery. She will be assisting with coordination of the study.

Alexis Rounds, BS is a medical student research fellow for the Department of Orthopaedic Surgery at the Keck School of Medicine of USC. She will be assisting with coordination of the study and is the main IRB contact person.

Erik Mayer, BS is a medical student research fellow for the Department of Orthopaedic Surgery at the Keck School of Medicine of USC. He will be assisting with coordination of the study.

Santano Rosario, BS is a medical student research fellow for the Department of Orthopaedic Surgery at the Keck School of Medicine of USC. He will be assisting with coordination of the study.

Alan Gurler, MS completed his Master of Science in Biokinesiology at the University of Southern California and has an Adjunct Faculty position in the Division of Biokinesiology & Physical Therapy.

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His main research interests are to better understand physiologic changes after the cessation of anabolic androgenic steroid use, and subsequently to restore normal function.

C. Thomas Vangsness Jr., MD is a professor in the Department of Orthopaedic Surgery at the Keck School of Medicine of USC. He specializes in the treatment and prevention of orthopaedic and sports-related injuries, including ACL reconstruction, meniscus surgery, cartilage repair and restoration, rotator cuff surgery and shoulder instability/dislocations. Dr. Vangsness is internationally recognized for his expertise in shoulder and knee surgery and has conducted and published extensive research with a focus on such topics as shoulder and ligament biomechanics, stem cell biology, allograft transplantation, and meniscal cartilage. Dr. Vangsness has been on the editorial board of several orthopaedic journals. He is a member of several organizations including the American Orthopaedic Society for Sports Medicine, American Shoulder and Elbow Surgeons, The Arthroscopy Association of North America, and the International Society of Orthopaedic Surgery and Traumatology (SICOT).

Seth Gamradt, MD is an Associate Professor of Clinical Orthopaedic Surgery at the Keck School of Medicine of USC and is a director of Orthopaedic Athletic Medicine for USC Athletics. Dr. Gamradt is on the editorial board of the journal *Techniques in Shoulder and Elbow Surgery*, and he is a Reviewer for the *American Journal of Sports Medicine* and the *Journal of Shoulder and Elbow Surgery* and is a member of many professional organizations, including: The American Shoulder and Elbow Surgeons (ASES), the Association of Clinical Elbow and Shoulder Surgeons (ACCESS), American Orthopaedic Society for Sports Medicine, Arthroscopy Association of North America, and the American Academy of Orthopaedic Surgeons.

James Tibone, MD holds the Moss Foundation Professorship in Sports Medicine in the Department of Orthopaedic Surgery at the Keck School of Medicine of USC and he is the medical director for USC's Athletic Department. Dr. Tibone is an internationally recognized expert in sports injuries of the shoulder, knee and elbow and total and reverse shoulder replacement surgeries and was the North American editor for the *Journal of Shoulder and Elbow Surgery*. He has served on numerous national professional committees, and is a past president of the American Shoulder and Elbow Surgeons.

Reza Omid, MD is an Associate Professor in the Department of Orthopaedic Surgery at the Keck School of Medicine of USC. He specializes in complex reconstruction of all shoulder and elbow conditions. He also has extensive experience in arthroscopic procedures and has pioneered several novel minimally invasive arthroscopic techniques for shoulder reconstruction. Dr. Omid leads the Shoulder & Elbow Trauma Service at LAC+USC Medical Center, one of the busiest Level 1 trauma centers in the nation. He is actively involved in research and has authored numerous articles. Dr. Omid is also involved in numerous national organizations including the prestigious American Shoulder & Elbow Surgeons (ASES) Society, the American Academy of Orthopaedic Surgeons (AAOS), and Arthroscopy Association of North America (AANA).

Lori Michener, PhD is a Professor of Clinical Physical Therapy and the Director of the COOR (Clinical biomechanics and Orthopedic Outcomes Research) Laboratory. As the Director of Clinical Outcomes and Research, she directs the development, collection, and analysis of patient-rated outcomes and the process of care in the USC Physical Therapy Associates Clinics, and serves as a resource for clinical research. Dr. Michener's research characterizes the biomechanics of musculoskeletal shoulder pain, diagnosis and treatment of shoulder and cervical pain, clinical trials investigating optimal treatment strategies for shoulder and cervical disorders, and the use of patient-rated outcomes measurement tools to assess health related quality of life.

4.0 Drug Information

Oxandrolone is an orally administered synthetic derivative of the hormone testosterone, and is classified as an anabolic steroid. In males, testosterone has many vital functions such as the development and support of reproductive organs, increased skeletal muscle mass, bone mineral density, and growth of facial and body hair.

Oxandrolone is approved by the Federal Drug Administration (FDA) in patients who have lost weight resulting from extensive surgery, severe trauma, chronic infection, or as an adjunctive therapy to promote weight gain. It is also approved for bone pain associated with osteoporosis, and to attenuate protein catabolism associated with the prolonged use of corticosteroids. Oral administration of Oxandrolone has demonstrated increases in lean mass, protein synthesis, and wound healing with no long-term adverse events in trauma patients as well as healthy male controls.¹⁻³ Elevated liver transaminase levels have been noted but have been transient and asymptomatic.¹⁻³ The aforementioned safety and efficacy profile of oral Oxandrolone makes it an appealing adjuvant treatment to counteract the major biologic consequences of a chronically torn rotator cuff (muscle atrophy, fatty infiltration, and intercellular fibrosis), which are known to lead to poor healing and diminished clinical outcomes.^{4,5}

Oxandrolone has been associated with the following side effects:

- Central Nervous System: Habituation, excitation, insomnia, depression, and changes in libido.
- Larynx: Deepening of the voice in females.
- Cardiovascular: Edema
- Breast: Gynecomastia.
- Hepatic: Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatis with long-term therapy (see US Boxed Warning below). Reversible changes in liver function tests also occur including increased bromsulphophthalein (BSP) retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).
- Genitourinary: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.
- Hematologic: Bleeding in patients on concomitant oral anticoagulant therapy.
- Metabolic/Endocrine: Decreased glucose tolerance, increased creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Inhibition of gonadotropin secretion.
- Fluid and Electrolytes: Retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).
- Musculoskeletal: Premature closure of epiphyses (in children).
- Dermatologic: Acne (especially in females and prepubertal males), hirsutism and male pattern baldness in females.
- Patients with moderate to severe COPD or COPD patients who are unresponsive to bronchodilators should be monitored closely for COPD exacerbation and fluid retention.

Contraindications: nephrosis, carcinoma of breast or prostate, hypercalcemia, pregnancy

US Boxed Warning:

Peliosis hepatitis: A condition in which liver, and sometimes, splenic tissue is replaced with blood-filled cysts which has occurred in patients receiving androgenic anabolic steroids. These cysts may be associated with hepatic dysfunction and even liver failure. This condition is usually completely reversible with cessation of drug.

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Liver cell tumors: Most often benign and androgen-dependent, however, fatal malignant tumors have occurred. Withdrawal of the drug often results in regression or cessation of tumor progression. Hepatic tumors associated with androgens and anabolic steroids are much more vascular than other hepatic tumors and may be silent until life-threatening, intra-abdominal hemorrhage develops.

Blood Lipid Changes: Changes associated with increased risk of atherosclerosis are seen in patients treated with androgens or anabolic steroids, including decreased high-density lipoprotein (HDL) and increased low-density lipoprotein (LDL).

Pregnancy: Oxandrolone is classified as Category X in pregnancy due to teratogenic effects including embryotoxicity, fetotoxicity, infertility, and possible masculinization of the fetus.

Breast Feeding: It is unknown whether Oxandrolone is excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from Oxandrolone, women who are nursing and do not wish to stop may not take part in the study.

5.0 Selection and Randomization of Subjects

Participants

Men and women, aged 40-75 years, presenting to an orthopaedic surgeon with a full thickness rotator cuff tear will be eligible for study screening. The inclusion and exclusion criteria are listed below.

All eligible patients will receive information about the trial verbally and in writing. After signing written informed consent, they will be randomly allocated to undergo rotator cuff repair followed by standard of care structured rehabilitation with Oxandrolone administration or standard of care structured rehabilitation with placebo. Allocation will be performed using computer software and will occur at the pharmacy to ensure that all investigators are blinded. The USC Pharmacy will prepare sequentially numbered, opaque, sealed envelope containing the assigned interventions to ensure randomness is preserved. The surgeon, PI, study team, and physical therapist will not know to which study arm the patient was randomized. The protocol for rehabilitation will remain the same for all patients. The USC Pharmacy will provide the investigators with a list of all participants and group assigned at the end of the study. Investigators will not have access to the study group assignment for any participant during data collection, to ensure adequate double-blinding of both the investigators and participants.

Inclusion criteria

- Men and women age 40-75 years old who have failed nonoperative management of chronic, full thickness rotator cuff tears confirmed by MRI without contrast

Exclusion criteria

- Patients with prior shoulder surgery or prior rotator cuff repair
- Tears larger than 5cm
- Significant glenohumeral arthritis (Hamada Grade 2 or higher)
- Untreated diabetes mellitus
- Pituitary tumor
- Rheumatoid Arthritis
- Uncontrolled hypertension
- Congestive Heart Failure
- Myocardial Infarction within the past 6 months

- End-stage renal disease
- Liver enzymes two times the normal value
- DVT within the past 6 months
- Disorder of the coagulation system
- Currently taking anticoagulation
- Claustrophobia
- Prior or current use of anabolic steroids
- Chromosomal disorders
- Prostate cancer
- Breast cancer
- Hypercalcemia
- Medications that interfere with testosterone production or function, including but not limited to 5 α -reductase inhibitors
- Pregnant or breastfeeding, or expecting to conceive **or father** children within the projected duration of the trial, starting with the Screening visit through **6 weeks** after the last dose of study treatment.
- Any other condition or treatment interfering with completion of the trial

6.0 Study Agent Administration and Safety

Oxandrolone Administration

Oxandrolone will be given to experimental men (12 mg BID) and women (6 mg BID) for 12 weeks starting the day of surgery. Previous clinical studies where oxandrolone was given for greater than 6 months have shown no androgenic effects, behavioral changes, sepsis, hirsutism, or acne in the patient population. Elevated liver transaminase levels have been noted but have been transient and asymptomatic.¹⁻³

Patient Safety and Compliance

Patients will have liver transaminase levels measured when preoperative labs are obtained. Additionally, liver enzymes will be assessed at 2, 6, 12, and 24 weeks after rotator cuff repair. Testosterone levels and a quantitative assay for oxandrolone will also be drawn prior to supplementation, at the 2 week post-operative visit and at the 6 month post-operative visit to assess for compliance. Any adverse medication reaction will be met with cessation of medication, but will continue to be followed for outcome data collection.

7.0 Clinical and Laboratory Evaluations

Program Time Line

Study participants will be tested on multiple occasions. Information will be collected prior to surgery, followed by measurements on the day of procedure, and 2, 6, 12, 24, 52, and 104 weeks after surgery. Surgery will be performed on an arranged date with the orthopaedic surgeon. Physical therapy will follow a pre-defined protocol with a physical therapist.

Testing Visits

Outcome measures and safety measures will be collected at routine postoperative visits with the operating surgeon. Dates and involved events are described in Table 1 below.

Schedule of Events

Event	Pre-Procedure	Procedure Day	Post-Operative Week					
			2	6	12	24	52	104
Informed Consent	x							
Demographics	x							
Confirm Inclusion/Exclusion Criteria	x	x						
Medical History	x	x						
Vital Signs	x	x	x	x	x	x	x	x
Randomization		x						
Blood draw: Testosterone level and Oxandrolone level	x		x			x		
Blood draw: Liver Enzymes	x		x			x	x	x
Outcomes:								
MRI: rotator cuff healing; Sugaya classification (primary outcome)	x				x		x	x
MRI: Fatty infiltrate (secondary outcome)	x				x		x	x
MRI: Muscle volume (secondary outcome)	x				x		x	x
Body Composition – lean mass & body fat (secondary outcome)	x		x	x	x	x	x	x
Questionnaires: ASES, VAS, PASS (secondary outcome)	x	x	x	x	x	x	x	x
Shoulder Range of Motion (secondary outcome)	x	x	x	x	x	x	x	x
Shoulder Strength (secondary outcome)	x	x	x	x	x	x	x	x

Table 1. Outline of pre- and postoperative timing of events and schedule of data collection.

Demographics.

Demographics of age, height, weight, race, arm dominance, and tear size and location will be recorded.

Inclusion and Exclusion Criteria.

The inclusion and exclusion criteria will be confirmed prior to enrolled, as described above in section 5.0.

Females of reproductive potential (women who have not been post-menopausal for at least 24 consecutive months, ie, who have had menses within the preceding 24 months, or women who have not undergone surgical sterilization, hysterectomy or bilateral salpingectomy or bilateral oophorectomy or tubal ligation) must have a negative serum or urine pregnancy test *with a sensitivity of ≤ 25 mIU/mL* within 48 hours prior to study entry.

Females of reproductive potential must agree not to participate in the conception process (ie, active attempt to become pregnant, in vitro fertilization), and if participating in sexual activity that could lead to pregnancy, must use at least one reliable form of contraceptive. Female subjects must use contraceptives *while receiving study treatment and for 6 weeks* after stopping study treatment.

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Acceptable forms of contraceptives include:

- *Condoms (male or female) with or without a spermicidal agent*
- *Diaphragm or cervical cap with spermicide*
- *Intrauterine device (IUD)*
- *Hormonal contraceptive*

NOTE: Written self-reported or partner reported sterility or lack of reproductive potential will be acceptable in place of contraceptive use.

Medical History.

A standard medical history questionnaire will be completed by the participant of past medical history of their shoulder pain, co-morbidities, and medical history of all other conditions.

Vital Signs.

Vital signs of temperature, blood pressure, respiration rate, and heart rate will be recorded.

Blood Draws

As described above, blood will be collected to monitor any adverse effects on the participant's health and to assess for medication compliance.

Outcomes:

MRI rotator cuff healing; Sugaya classification (Primary outcome). All participants will have a standardized MRI T2-weighted images without contrast, and used to classify rotator cuff integrity using 5 categories of the Sugaya classification. The 5 categories are: type I= rotator cuff sufficient thickness with homogeneously low intensity on each image; type II= rotator cuff sufficient thickness, partial high-intensity area; type III= insufficient rotator cuff thickness with less than half the thickness as compared to normal cuff, but without discontinuity; type IV= minor rotator cuff discontinuity with only 1 – 2 slices on imaging that suggest a small full-thickness tear; and type V= major discontinuity observed in more than 2 slices on imaging, suggesting a medium or large full-thickness tear.³³

MRI: Fatty infiltrate (Secondary outcome). All participants will have a standardized MRI T2-weighted images without contrast. The Goutallier grading classification⁷ will be used to assess fatty infiltration on 5 categories of grade 0= no fatty infiltration; grade 1= some fatty streaks; grade 2= less fat than muscle; grade 3= as much fat as muscle; and grade 4= more fat than muscle.

MRI – muscle volume (Secondary outcome). All participants will have a standardized MRI T2-weighted images without contrast, using the scapular plane of the sagittal-oblique image to measure supraspinatus muscle volume. Muscle volume will be measured by tracing the outer borders of the muscle, expressing the volume in mm^{2,34}.

Body Composition (Secondary outcome),

Study participants' lean mass and body fat percentage will be measured by bioelectrical impedance using Biospace InBody. The participant will have measurements at their preoperative visit and all postoperative visits.

Questionnaires (Secondary outcomes).

The participant will be asked to complete 3 questionnaires. Two questionnaires will be used to assess shoulder pain and function; American Shoulder and Elbow Surgeons Shoulder Assessment (ASES) to assess the patient-rated shoulder function on a scale of 0 -100 (0= no shoulder function/ disability), and a

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Visual Analog Pain Scale (VAS) to assess the level of pain on a scale of 0 -10 (0 = no pain).¹¹⁻¹³ Patient satisfaction will be assessed with a single item question labeled the patient acceptable symptom state (PASS) questionnaire.^{11,14,15} The PASS is a 2-item question asking the patient their opinion of their current state of their shoulder, and if it is satisfactory for them. ASES, VAS, and PASS questionnaires at each visit to assess clinical outcomes.

Shoulder Range of Motion and Strength (Secondary outcomes).

Shoulder range of motion of flexion, abduction, external and internal rotation will be measured. During active range of motion, patients will be asked to move the shoulder as much as they can in the direction indicated by the investigator. Once participants reach their maximum range of motion, the measure will be recorded with a goniometer in degrees of motion. Two measures will be taken for each direction, and averaged for data analysis.

Shoulder strength will be measured using a hand-held device of: shoulder flexion, elevation on the scapular plane (scaption), external rotation, and internal rotation. The hand-held device (Hoggan Health Industries Inc., West Jordan, UT) is small device that contains a force transducer, measuring strength in kg of force. It is also commonly used in clinical settings, as it allows for accurate, and reliable measure. The arm of the patient will be positioned in a similar set of positions. The device will then be placed in contact with the distal segment. Participants will be asked to push against the device as hard as they can. Two measures for each movement will be collected. One-minute rest will be provided between measures.

Treatment

Orthopaedic Surgery

Rotator cuff repair will be performed by fellowship trained orthopaedic surgeons listed above.

Physical Therapy

Rehabilitation will follow a standard guideline under the supervision of a licensed physical therapist and the participant's physician.

8.0 Criteria for Evaluation and Endpoint Definitions

Outcome Measures

The primary outcome measure will be rotator cuff healing as measured by the MRI Sugaya classification.^{6,7} Measures will be performed at 12 weeks (the conclusion of Oxandrolone vs. placebo treatment), 6 months, 1 year and 2 years follow-up. The primary end-point will be 6 months.

Secondary outcome measures will include:

- 1) MRI evidence of rotator cuff fatty infiltration and muscle volume.
- 2) Patient-reported outcomes will be assessed with the ASES, a VAS, and PASS questionnaire.
- 3) Functional outcome will be assessed with shoulder range of motion with goniometer and isometric shoulder strength measures using a handheld dynamometer
- 4) Lean body mass and fat will be assessed with bioelectric impedance.

9.0 Data Collection and Monitoring

The research coordinator, employed by the Department of Orthopaedic Surgery, will be responsible for patient enrollment and data collection. Source documents will be stored in an office in a locked cabinet within the Department of Orthopaedic Surgery. Data will also be collected and stored using CTSI RedCap.

10.0 Statistical Considerations

Statistical Methods

Descriptive statistics will be performed for participant demographics, historical information, intraoperative variables, as well as baseline testosterone, MRI measures of rotator cuff integrity, rotator cuff fatty infiltrate, rotator cuff muscle volume, shoulder strength, shoulder range of motion, patient-rated outcomes and body composition. Comparison for the primary outcome measure of rotator cuff integrity between groups from baseline to 1 year (primary endpoint) will be performed using a repeated measures analysis of Generalized Estimating Equation (GEE), appropriate for ordinal data. The GEE will also be used to compare between groups over time for the secondary outcome of fatty infiltrate (ordinal data). For all other secondary outcome variables, we will also use GEE for linear regression (ordinal data) or mixed model (continuous data) with repeatedly measured outcomes. Significance level will be established as $p < 0.05$. Analyses will be performed using STATA 13 software (College Station, TX) or SPSS and in consultation with the Statistics Department at USC.

Power Analysis and Sample Size

A power analysis for a sample size estimation was performed to detect a difference of 1 Sugaya grade (1-5 grades) classification (primary outcome) between the experimental and control group using 3 repeated measurements (baseline, 12 week, and 6 months).¹⁴ The power analysis was based with 2-sided alpha = 0.05 and power of 80%, and assuming a correlation among the repeated measures of 0.7 and overall SD of 2, giving a minimum sample size of 104 participants (n=52 participants in each group). This corresponds to an ANOVA effect size of 0.28 (28% of variance in primary outcome explained by treatment effect), or alternatively a moderate Cohen's D effect size (group mean difference divided by SD) of 0.5. Oversampling by 10% to account for possible attrition yields a total of 116 participants with 58 per group.

11.0 Registration Guidelines

At time of registration, two copies of a signed and dated participant's Informed Consent form with Bill of Rights must be available (an original for patient's medical chart; one copy for the patient, one copy for the research records)

12.0 Biohazard Containment

Biohazard materials will be disposed of properly in the clinic. Blood will be stored safely and securely until analysis.

13.0 Ethical and Regulatory Considerations

All institutional and Federal regulations concerning the Informed Consent will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

14.0 References

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