RESEARCH PROTOCOL

Title:	The Comparison and Combination of Semiconductor Embedded Therapeutic Arm Sleeves and Platelet-Rich Plasma with Adipose Stem Cell (PRP+ASC) Injections for the Treatment of ECRB Tendinopathy (Lateral Epicondylitis): A Randomized, Double-Blinded, Placebo-Controlled Prospective Clinical Trial
Protocol Date:	28, August 2024
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1. STUDY SUMMARY

Extensor Carpi Radialis Brevis (ECRB) tendinopathy, also known as lateral epicondylitis or tennis elbow, is the most prevalent elbow soft tissue injury and affects 1-3% of the population[1]. Repetitive overloading of the tendon and ligaments in the elbow lead to microtraumas, causing abnormal angiofibroblastic remodeling and increased pain[2]. Microtearing occurs most commonly at the origin of the extensor carpi radialis brevis (ECRB) tendon. The main symptoms include a loss of grip strength, a burning sensation near the ECRB origin site, and pain during daily activities such as grasping objects or shaking hands[3]. Both conditions present a significant injury and treatment burden on the population and effective treatment and pain management approaches with minimal side effects are needed.

Novel nonsurgical treatment approaches for ECRB tendinopathy include platelet-rich plasma (PRP) injections and stem cell therapy. Ultrasound-guided PRP and adipose-derived stem cells (ASCs) injections have shown to be an effective treatment option for patients with chronic ECRB tendinopathy[4,5,6,7].

The proposed study seeks to assess the effect of non-compressive semiconductor embedded arm sleeves in combination with PRP + ASC injections, throughout a 6-month rehabilitation course for patients with ECRB tendinopathy. Outcome measures will be collected at standardized intervals to evaluate and compare treatment groups.

2. BACKGROUND

Unlike compression products, the semiconductor embedded fabric increases blood circulation through activation of the embedded elements with heat of the body[8] and releases mid and far infrared waves as well as negative ions. Both infrared waves and negative ions are biologically active and mediate inflammatory and pain pathways in the body[9]. The technology has also been shown to:

- Increase blood flow and velocity[10]
- Reduce osteoarthritis pain[8]
- Reduce effusion post total knee arthroplasty[11]
- Improve chondrogenic differentiation *in vitro*[12]
- Improve muscle recovery[13]
- Increase circulation by up to 22% at rest[10]
- Improve functional outcomes[8, 11]

The benefits of the Infrared Wave and Negative Ion therapy include:

- Inhibition of Cox-2 and Prostaglandins in the lipopolysaccharide (LPS)-moderated pain pathway[14]
- Up-regulation of heat shock protein[14]
- Mediated Nitric oxide production[15]
- Increased activity of voltage-gated ion channels[14]
- Increased activity of mechanosensitive ion channels[14]

- Polarization of cell surface membranes[14]
- Protecting muscle damage[16]
- Scavenging of Reactive Oxygen Species (ROS)
- Improved thermoregulation[17]

To date, studies have shown that the semiconductor embedded fabric increase circulation by up to 22% at rest, and have shown powerful results in reducing inflammation, swelling, improving range of motion in the knee post-surgery, and providing pain relief to the joints.

The semiconductor embedded fabric emits mid-level and far infrared waves and negative ions. Delivery of infrared waves and negative ions to the tissue increases circulation of both blood and lymph, facilitates the anti-inflammatory nitric oxide (NO) cascade by accelerating the binding of calcium (Ca^{2+}) to calmodulin (CaM)[15]. NO provides several healing factors to the body, increasing blood and lymphatic flow[15]. Additionally, NO down-regulates interleukin-1 beta (IL1β) and inducible nitric oxide synthase (iNOS) in certain cell types, which leads to reduced cyclooxygenase-2 (COX-2) and prostaglandins – molecules responsible for causing inflammation and pain. Unlike other systemic COX-2 inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs), targeted infrared and negative ion therapy stimulate localized reaction pathways, thereby reducing pain and inflammation.

This study seeks to identify patient reported and clinically measured outcomes for pain management and elbow function with application of semiconductor embedded fabric combined with PRP+ASC injections in the affected area.

3. OBJECTIVES

1. Determine the effect of the semiconductor embedded arm sleeves on patient reported and clinically measured outcomes in patients with ECRB tendinopathy.
2. Evaluate the change in symptoms in patients following treatment with the semiconductor embedded arm sleeves.

4. HYPOTHESIS

Subjects who are assigned and compliant to wearing the semiconductor embedded arm sleeve will experience improved outcomes in symptoms, pain management, and elbow function throughout the course of the study compared to the patients assigned to wear and compliant with wearing the placebo sleeves.

Primary Endpoint

Completion of 8 weeks wearing the semiconductor embedded arm sleeves with at least 80 subjects.

Secondary Endpoint

Completion of 6 months wearing the semiconductor embedded arm sleeves with at least 80 subjects. Additional subjects may be required to enroll in the study to achieve a total of 80 subjects who complete all outcome measures for 6 months.

Primary Outcome

Improvement in patient function in patients using the semiconductor embedded sleeve compared to placebo as measured by PRTEE.

Secondary Outcomes

1. Reduction in pain as determined by Numeric Pain Rating Scale or Visual Analog Scale (VAS) compared to placebo group.
2. Improvement in patient function as determined by Patient Specific elbow PROMIS score (Disabilities of the Arm, Shoulder, and Hand (DASH) and Patient-Rated Tennis Elbow Evaluation (PRTEE)) and the patient specific functional score compared to control and placebo groups.
3. Reduction in symptom severity upon physical examination and improvement in grip strength compared to placebo group.

5. STUDY DESIGN

The study will be prospective, randomized, and double-blinded with at least 80 subjects that will be recruited by the principal investigator (PI). Patients meeting enrollment criteria will undergo an informed consent discussion prior to any study activity.

Subjects meeting enrollment criteria and consenting to participation will undergo a 6- month trial.

Study groups:

a. Among participants who opt out of receiving PRP+ASC injections as part of their routine medical care:
    i. One group will receive active therapy (semiconductor embedded arm sleeve) “Incrediwear only”
    ii. One group will receive placebo therapy (arm sleeve absent of semiconductor thread) “Sham Incrediwear”
b. Among participants who choose to receive PRP+ASC injections as part of their routine medical care:
    i. One group will receive active therapy with SOC PRP+ASC injections (active semiconductor embedded arm sleeves after they have received PRP+ ASC injections as part of their routine care) “Incrediwear with SOC PRP+ASC injections”
    ii. One group will receive placebo therapy with SOC PRP+ASC injections (arm sleeve absent of semiconductor fabric after they have received PRP+ASC injections as part of their routine care) “Sham Incrediwear with SOC PRP+ASC injections”

Subjects will determine whether they would like to receive Standard of Care (SOC) PRP+ASC injections. Then, the subjects will be randomly assigned to the study group in which they will receive a real or sham semiconductor embedded sleeve. The subjects will be instructed to wear the sleeve for a minimum of 12 hours per day, including overnight, for the entire duration of the study.

Patients will determine whether to receive PRP+ASC injections independent of their participation in this research study. Then, they will be assigned to a study group and will either receive a real or sham sleeve. Study groups will be blinded, randomly assigned, and block randomized based on the severity of ECRB tendinopathy (lateral epicondylitis). Severity of ECRB tendinopathy will be ranked as mild, moderate or severe as follows:

Mild – tendinopathy with no visible tearing of ECRB tendon.

Moderate – visible partial tear of ECRB tendon, less than 50%

Severe – greater than 50% tear, but less than 100% tear of ECRB tendon.

All subjects participating in the study will also be assigned to the standard physical therapy routine, *without* direct interventions including dry needling, Graston blading, laser therapy or iontophoresis.

Inclusion Criteria

1. Patients diagnosed with ECRB tendinopathy as determined by radiographic assessment or ultrasound imaging.
2. Patients age 18-65
3. Patients who are willing and able to adhere to follow-up schedule and protocol guidelines.
4. Patients who are willing and able to sign corresponding research subject consent form.

Exclusion Criteria

1. Patient has a history of neurological conditions, including multiple sclerosis or Parkinson's disease
2. Patient has severe medical condition, including recent myocardial infarction, unstable angina, heart failure, severe anemia
3. Patient has had prior surgical treatment of the elbow in the last 5 years or injection treatment(s) in the last 2 years
4. Patient has complete tear of ECRB tendon or other surgical indication
5. Patient has chronic pain conditions unrelated to elbow condition
6. Patient has auto-immune or auto-inflammatory diseases
7. Patient has used tobacco within the last 90 days
8. Patient is not within the ages of 18-65
9. Patient has a history of metabolic disorders
10. Patient has an active infection (local or systemic)
11. Patient is unwilling or unable to sign the corresponding research subject consent form

12. Patient meets any other criteria or has any other condition that, in the opinion of the investigator, would prevent them from completing the study or that, in the opinion of the investigator, would confound study results.

Study Measures

Subjects will complete a variety of repeated subjective and objective measures throughout the course of the study. A schedule of study-related events can be found in Table 1.

TABLE 1	Enrollment Visit	2-Week Follow-Up Phone Call	4-Week Follow-Up Phone Call	8-Week Follow-Up Visit	3 Month Follow-Up Phone Call	6 Month Follow-Up Visit	*Daily Reported
Enrollment Screening	X						
Informed Consent Discussions	X						
PROM Scores[18, 19]	X	X	X	X	X	X	
Numeric Visual Analog Scale[20]	X	X	X	X	X	X	X
Patient Specific Functional Score[21]	X	X	X	X	X	X	
PFG Measurement (Grip Strength Test)[22]	X			X		X	
Device Usage Log							X
Medications Log							X

*Daily reported measures will only be required up to the 8-week timepoint.

Description of Measures

Enrollment Screening: Patient demographic information, past medical history, weight, history of pain, prior treatments, and any secondary diagnoses will be recorded to ensure the patient is a candidate for the trial.

Informed Consent Discussion: Doctor or study staff will explain the research, go through corresponding research subject consent form, and answer patient questions.

(Disabilities of the Arm, Shoulder, and Hand (DASH) and Patient-Rated Tennis Elbow Evaluation (PRTEE))[18,19]: Patient will report the difficulty in performing various activities, elbow-related quality of life, and the level of pain experienced in the previous week.

Visual Analog Scale (VAS)[20]: Patient will self-report pain level in the shoulder on a 0-10 scale at the same time each day for consistency.

Patient Specific Functional Score[21]: Patient will identify and score up to three important activities they are unable to do or have difficulty doing due to elbow injury.

Hand Grip Strength Test[22]*:* Doctor or study staff will measure the patient's grip strength with a dynamometer.

Device Usage Log: Patient will self-report device usage, including time of therapy initiation, time of therapy completion, and device location.

Medications Log: Patient will self-report medication intake, including type and quantity.

Statistical Analysis

Relevant clinical variables and demographic characteristics will be summarized by standard descriptive summaries (e.g. means, standard deviations, minimums, maximums, confidence limits, percentiles).

6. COMPLIANCE STATEMENT

This study will be conducted in full accordance with all applicable Federal and State laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented. The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unanticipated problems involving risks to subjects or others in accordance with Western IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after completion of the study.

7. RISK AND SAFETY MANAGEMENT

This study utilizes a treatment with no demonstrated side effects. There is minimal risk involved with the treatment or evaluation of the subject associated with this study. The primary risk in this study is the identification of individuals. However, all project staff with access to study data are accustomed to working with PHI-related, identifiable data and have completed requisite human subjects and data protection training. Additionally, safeguards are in place that will limit access to project folders to only the individuals directly involved with data collection and analysis. Data are stored in a secure electronic folder on the PI's server, and patient identifiers will be securely stored

separately from other information in data sets. The data collected for the study will be stored in a secure electronic database to which only the investigators will have access. Data analysis will occur using de-identified methods.

Monitoring/Reporting of AE/SAE

The adverse events associated with PRP injections include skin reaction and local injection site pain. There is minimal risk with the semiconductor sleeves and as such we do not expect any adverse events. The main risk with this type of study is breach of confidentiality through the potential identification of individuals included in the study. If a breach of confidentiality occurs, the principal investigator and the project team will work together to report it to the compliance office and IRB and will follow the appropriate procedures. However, all standard procedures will be followed to ensure data privacy is maintained, i.e., by storing data in a limited access secure folder that is on the PI's server.

Study Oversight

If study data are requested for monitoring, auditing, or regulatory inspection, the principal investigator will provide them in a timely manner. The study investigators will address all possible concerns and safety issues are not anticipated. There are no reasons why this study would need to be prematurely terminated and therefore oversight is not applicable.

Data Management

All study related data will be stored in a limited access folder that is on the PI's network. Some analysis of de-identified data may be conducted by Sponsor consultants, all of whom completed requisite human subjects and data protection training. All analysis will be conducted using Microsoft Excel or SPSS version 25.

IRB Review/Ethics/Informed Consent

All potential participants will be provided a research subject consent form and time with their doctor to go over this form. Only subjects who are willing and able to sign the consent form will participate in the study. Subjects may choose to opt out of the study at any time and will be informed of this. Data collected for this study will be obtained from the patient electronic medical record (EMR), questionnaires completed by the subject, and in case report forms completed by the PI or study staff. This study is being conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study is being conducted in accordance with applicable regulations, applicable laws and the IRB requirements. The investigators will submit any change to the protocol to the IRB for review and approval before implementation.

Confidentiality

Only members of the PI's study team will have access to identifying data as part of this study. All involved staff at the PI's institution routinely work with patient data for purposes of clinical care and/or research and as such will follow standard procedures for protecting data privacy. All study related data will reside in secure, password-protected databases and folders with access limited to the people conducting data collection and analysis. All patient identifiers will be securely stored separately from other information in data sets and these identifiers will be eliminated from data sets after analysis is complete and results are published. All study records identifying the subjects will be kept confidential and will not be made publicly available or presented in any publications. Any monitor, auditor, IRB and/or other regulatory authorities will have access to the existing dataset on which these analyses will be based. The datasets will contain medical record information, but will not be directly linked to the record in its entirety.

Intended Use of the Data

Data will be stored and used for the duration of time required to conduct analysis and publish all proposed peer-reviewed papers, according to study objectives. Data will be retained for 2 years after publication to allow for re-analysis that may be initiated in response to readers/reviewers. Subject records will be maintained at the PI's clinical site for a minimum of 7 years following latest study follow-up.

8. REFERENCES

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