Internal brace augmented anterior inferior tibiofibular ligament repair and its post-operative effects on syndesmotic volumes: A prospective, single-blinded, randomized study

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Protocol ID: IIRR-01161

Clinical Trial Registration: NCT05062265

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1. BACKGROUND, OBJECTIVES, & STUDY DESIGN

Ankle syndesmosis disruption due to ankle trauma is associated with significant pain and disability.[1,2] Surgical stabilization procedures typically involve an internal fixation of the distal tibiofibular joint to restore the spatial relationship of the bony structures. Rigid fixation has traditionally been the technique of choice for stabilizing the syndesmosis; however, dynamic fixation options like the TightRope® system (Arthrex®, Naples, United States) have more recently demonstrated some advantage over rigid screw fixation techniques as they attempt to mimic the dynamic nature of the syndesmosis.[3-6] Tightrope or flexible fixation is still a non-anatomic reduction and stabilization technique and as such is only an approximation of the syndesmotic ligaments.

Anterior inferior tibiofibular ligament (AITFL) augmentation techniques using nonabsorbable suture materials (*Internal*Brace, Arthrex®, Naples, United States) have been used to supplement syndesmotic fixation in order to more accurately reconstruct the syndesmosis and restore native biomechanics.[7,8] Clinical research assessing the use of the *Internal*Brace as an additional stabilization method is lacking and the minimum required stability to achieve successful clinical and patient-reported outcomes remains unclear.

The primary objective of this study is to evaluate the quality of syndesmotic reduction as determined by weight bearing 3-D relative volumetric ratio between ankles in patients undergoing syndesmotic stabilization with and without an *Internal*Brace augmented repair of the AITFL to determine if the technique influences the reduction and postoperative stability of the syndesmosis. This will be compared at both 6-weeks and 3-months post-operation. Our

secondary objectives are 1) to determine whether the addition of the *Internal*Brace augmentation to the traditional TightRope fixation procedure improves short- and long-term patient-reported ankle function and generic health ratings and 2) to explore relationships between syndesmotic volume and patient-reported outcomes across groups.

Design

We will use a prospective, two-arm, single-blind, randomized study design to conduct our pilot study. After informed consent, twenty patients will be randomized evenly into a traditional TightRope fixation group or a TightRope fixation with an AITFL augmentation group upon enrollment into the study. As this is a pilot study with a small sample size, block randomization will be used to reduce the risk of unequal group sizes between groups. A researcher who will not otherwise be involved in patient interactions will serve as the randomization coordinator for this trial. They will prepare a randomization schedule using the freely accessible tools available at www.randomization.com. The sequence generator uses block randomization procedures based on the number of interventions and patients needed in each block and creates a schedule based on the patient ID number. Due to the potential emergent nature of injuries involved in this study and a short time between enrollment and surgery, the surgeon may need to acquire the group allocation shortly after enrolling patients to be able to prepare for the surgery and so the schedule will be converted to a Google Document that can then be accessed by the surgeon/PI to reveal the intervention allocation. Since pre-operative and post-operative instructions are the same regardless of the procedure, the participants will be blinded to their intervention group until the completion of the study period.

Participant Population

Due to the nature of the study population needed, potential participants will be recruited from the clinic or corresponding hospital of the study doctor. Patients will be considered for inclusion in the study if they are over 18 years old and demonstrate unilateral ankle trauma causing syndesmotic disruption (e.g., ligamentous rupture, and/or bimalleolar and trimalleolar ankle fractures) and are determined to be good candidates for TightRope fixation surgery outside of the research context. Exclusion criteria is as follows: Illiterate patients, non-English speakers, minors, patients with diminished mental capacity, or any patient needing a legally authorized representative, pregnant patients, patients that have had a previous ankle surgery, have an open fracture, fractures that require posterolateral approach, or any contralateral foot or ankle injury. I Additionally, patients will also be excluded if they are unable to complete the CT scans necessary for completing the volumetric assessments, or if upon surgical exposure, the AITFL remains intact. In the case of the latter, the patients would still receive appropriate procedures necessary for treating their ankle trauma but would be excluded from the study.

Participant Enrollment and/or Screening

Patients will be identified in the clinic or hospital by the study doctor. Patients will be consented for syndesmotic open reduction surgery using the TightRope system which will indicate the patient for potential inclusion into the study. Patients will then be screened for exclusion criteria listed above and if no exclusion criteria are present, the patient would be considered for inclusion and the informed consent process would begin.

Withdrawal of Subjects

Participants will be withdrawn from the study if any of the following conditions exist:

1. Participant voluntarily withdraws from the study
2. Participant death

3. Participant who, in the opinion of the PI, would be compromised by continued study participation
4. Participant experiences an AE that, in the opinion of the PI, necessitates removal from the study, including unresolved SAE or death
5. Participant experiences an intercurrent illness, injury, or other reason that would, in the opinion of the PI, affect the assessment of clinical outcomes or the conduct of the study to a significant degree
6. Participant fails to comply with protocol requirements
7. Administrative reasons (e.g., PI decides to discontinue the study)

Under these conditions, all patient data will be immediately destroyed. During the consent process, participants will be informed of their right to withdraw from the study at any time for any reason and without prejudice to alternative treatment. For subjects lost to follow-up, the research team should attempt to contact the patient via phone a minimum of three times before considering them lost to follow-up. Participants who withdraw voluntarily or are discontinued by the PI will remain eligible for standard of care treatment by the PI and research team.

2. STUDY PROCEDURES

Prospective patients will enter the clinic or hospital associated with the study doctor seeking care after ankle trauma. Patient will be moved through clinic/hospital workflow as normal. Once the patient elects to undergo syndesmotic stabilization surgery and is over 18 years of age, study protocol will be triggered as follows:

1. The study doctor will do an initial clinical screening for open fractures or fractures that would require a posterolateral approach during his examination, and if present, the patient will be excluded. If patients are not excluded at this point, the study doctor or another

member of the research team will enter the room and work through the informed consent process with the goal of obtaining the consent. Patient will have ample opportunity to read through documents to their desire. Patient will be asked if they are literate and speak English comfortably and excluded if they do not answer yes to both questions.

2. Once the consent is signed, a research team member will review patient's medical history for presence of other exclusion factors: previous ankle surgery, or any contralateral foot or ankle injury. If any exclusion factor is present, consent documents will be shredded.
3. If no exclusion factors are present at this point, the following will occur:
    a. The patient will be issued a participant ID number and will complete the pre-operative patient-reported outcomes (PROs) related to their perceived ankle function (The Foot and Ankle Outcome Score) and generic health status (SF-36). These will be administered by a research team member by using either paper format, or a tablet computer through a survey administration software called Surgical Outcome System (SOS).
    b. The participant ID will be used by the study doctor to verify their randomized group allocation schedule generated by block randomization procedures described above and will be scheduled for their respective surgery.
4. Patient will follow typical pre-operative procedures. During the procedure, the patients will be in a supine position so that the fibula and the lateral ankle ligaments can be exposed. The integrity of the AITFL will be examined by the study doctor, and if disrupted the participant will be included in the study and will undergo either the traditional TightRope fixation procedure or the double stabilization procedure (TightRope fixation plus *Internal*Brace augmentation) as assigned and performed by the

study doctor. If AITFL disruption is not confirmed at this point, the patient will be excluded from the study; however, will still undergo the appropriate stabilization procedures necessary for treating their traumatic injury. If patients are excluded at this point, they will be informed post-operatively, and all study documents will be shredded.

5. If participants are not excluded and are assigned to the traditional TightRope fixation group: the fibular fracture will be stabilized with fixation and the plate will be applied laterally to the fibula. The syndesmosis is directly reduced and held in a stable position with the TightRope device. The syndesmosis is then restressed and examined to ensure that it is stable and reduced.
6. If participant is not excluded and is assigned to the TightRope fixation plus *Internal*Brace augmentation group: the FiberTape portion of the *Internal*Brace will be threaded through the distal fibular plate which will then be applied. The fibular fracture will be stabilized with fixation and the plate applied laterally to the fibula. The syndesmosis will be directly reduced and held in a stable position with the TightRope device. A 3.4 mm drill and 4.75 mm tap are used to make a small hole in the distal tibia at the anatomic origin of the anterior inferior tibiofibular ligament. A 4.75 mm SwiveLock anchor is then used to set the tension of the AITFL repair over the top of the torn AITFL ligament. The syndesmosis is then restressed and examined to ensure that it is stable and reduced.
7. Pre-operative PRO data for all eligible participants will be entered into a spreadsheet by a research team member along with basic demographic information (age, biological sex, height, weight, race), involved side (right or left ankle), type of procedure (traditional or traditional plus augmentation), and any relevant surgical notes.

8. All participants will be given the same post-operative directives regarding treatments and care which includes being non-weightbearing and immobilized for the first two weeks after surgery. At this point, the patients will begin a physical therapy program incorporating passive modalities and gentle range-of-motion exercises. Patients will remain non-weightbearing in a post-operative cam boot for the next 4-6 weeks.
9. Participants will then return to the office for their 6-week and 3-month follow-up visits where they will complete the PROs and the bilateral WBCT using the CT Lineup (CurveBeam, Warrington, PA) which will be used to determine 3D syndesmotic volume. Participants will be followed throughout the remaining study period and will complete the PROs again at 6 months and 1 year post-operatively. PRO data will be entered into the study spreadsheet by a research team member after each of these follow-up visits.
10. At the duration of the study period patients will receive the details of their surgery group to have for their records and knowledge.
11. Deidentified data will be analyzed by one of the study coordinators (AS) at the completion of data collection.

Consent Process and Documentation

The study doctor or another research team member will complete the entire consent process. Potential participants will be identified in the clinic or hospital. Once the subject has signed the surgical consent, the study will be presented and explained to them. After receiving detailed information regarding the study, objectives, logistics, inclusion/exclusion criteria, risks and potential benefits, they can then choose to sign the consent form once all their questions have been answered. The signed consent form will represent documentation that the consent process took place. The documentation will be stored in a locked file cabinet in the secured

research office. Patient will be informed that: data will be kept in excel spreadsheets only accessible to authorized study personnel on password protected computers; Identifiers will be kept until the end of the study, and data will be destroyed at the soonest possible time; Identifiers and data will be kept for the study period and only necessary personnel will have access to data.

3. OUTCOMES & DATA

Primary Outcomes

3D Syndesmotic Volume: Volumetric assessment of the distal syndesmosis will be performed with the WBCT using the CubeView software (CurveBeam, Warrington, PA). The software can calculate 3D volume amounts using cross-sectional imaging.[9] Measurements will start from the joint line and extend proximally,[9-11] and will be performed by research staff blinded to the surgical procedure and trained by the study doctor.

Patient-Reported Outcomes:

- The Foot and Ankle Outcome Score (FAOS) will be used to assess participants' perceived ankle function.[12] It is a 42-item questionnaire with five subscales measuring pain, other symptoms including swelling, stiffness and range of motion, activities of daily living, sport and recreation, and foot and ankle-related quality of life and has demonstrated high internal consistency with subscales ranging from α = 0.88-0.97, acceptable test-retest reliability, and validity.[12] Items are scored on a 5-point Likert scale from *no* to *extreme*. Scores are totaled for each subscale and transformed into percentages, with 100% being representative of no functional loss.
- The SF-36 will be used to assess generic health ratings as it has demonstrated good reliability (ICC = 0.87) and construct validity.[13] It is a 36-item questionnaire

assessing physical functioning, social functioning, role limitation caused by physical problems and emotional problems, bodily pain, mental health, energy, and general perceptions of overall health which combine to form the physical component summary (PCS) and the mental component summary (MCS).[13] The norm-based standardized versions are based on a population mean of 50 and a standard deviation of 10 and will be used for analysis to allow for easy comparison with population norms.

Adverse Events (AE) Definitions & Reporting

The research team will collect all adverse events (AE) during the study from the time of enrollment until the patient exits the study. The following definitions are intended to assist the research team in the identification of AEs. The research team will follow applicable regulatory requirements to report AEs to regulatory authorities and to the IRB.

Adverse Event (AE): An AE is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study whether it is related or unrelated to the investigational device or its use. An AE need not be symptomatic to be reportable, e.g., device disruption detected on imaging that would require treatment, or psychological distress or discomfort associated with survey instruments.

Serious Adverse Event (SAE): An SAE is any AE that is:

- **Fatal**
- **Life threatening:** the participant is at risk of death (could have died without intervention) at the time of the event. This does not apply to any *hypothetical* risk of death if the AE were more severe or were to progress.
- **Require or prolongs a hospital stay:** Greater than 1 day (24 hours)

- **Permanent impairment to a body structure or body function**

Relationship of AE to the study: The relationship of the AE to the study devices or procedures will be classified as either:

- **Related**: The adverse event has a reasonable temporal relationship to the use of the device or the procedure and cannot reasonably be explained by known characteristics of the participant's clinical state or other therapies.
- **Not Related**: The adverse event is due to the underlying disease state or is due to concomitant medication or therapy not related to the use of the device.
- **Unknown**: If the adverse event cannot be determined to have a causal relationship, it will be classified as unknown.

Unanticipated: The sponsor is responsible for classifying AEs as anticipated or unanticipated according to the accepted regulatory definitions.

The PI and research team will be responsible for ensuring participants' safety daily and for the reporting of any SAEs and unanticipated AEs that are determined relevant to the devices or study procedures. For reportable events, the research team will follow applicable regulatory requirements to report the event to regulatory authorities and to the IRB immediately.

Data and Safety Monitoring Plan

Investigators and research staff will make every effort to maintain confidentiality. Once patients consent and are enrolled into the study they will be given a participant ID number that will be used to track and identify them for the remainder of study. Only those directly involved in the research will have access to the document matching the participant's name with participant ID number. Electronic data will be de-identified and stored on an encrypted and secured network drive which is only accessible to the research team. All paper files will be stored in a secured and

locked filing cabinet only accessible by research staff at 1975 Glenn Mitchell Dr, Suite #200 in the research office.

All study personnel will be responsible for knowing the protocol and adhering to the protocol. Study personnel will self-check and review the protocol frequently to ensure they know it very well. If a study team member is found to deviate from the protocol, the member will be warned and reminded of the protocol. If this occurs multiple times, the member will be removed from the study and the mistakes reported to the IRB. Changes to protocol will not be implemented until approved by IRB.

STUDY RISKS & BENEFITS

Potential Risks to Study Participants & Risk Mitigation

1. Potential Risk: Loss of confidentiality
    - Risk Mitigation: All reasonable barriers will be in place to protect against the potential loss of confidentiality:
        i. Data will be de-identified and data collection tools used to collect participants data will use unique subject ID numbers for identification
        ii. Only generic demographic variables (e.g., age, sex, race) needed to evaluate participant characteristics will be captured in data collection
        iii. Study materials and data collection tools will be kept in secure, locked areas only accessible to research team
        iv. Electronic spreadsheets will only be accessible to assigned authorized personnel and will be password protected
        v. Imaging (e.g., CT scan) will only be accessible by PI and clinical staff, and will be de-identified and labeled with subject ID numbers before

volumetric assessments are completed

vi. Study records will be continually monitored by study coordinators to ensure all data is de-identified. Any oversights will be corrected and research team members will be notified.

2. Potential Risk: Harm from radiation exposure during weight-bearing CT scan
    - Risk Mitigation: All reasonable limitations and protections against potential adverse health effects that may be associated with radiation exposure will be in place:
        i. Patients that are not able to complete the WBCT necessary for volumetric assessments will be excluded
        ii. During the consent process, the research team and the participant will discuss and assess the participant's exposure history and determine if the potential risk is acceptable for that participant. The participant will be given the opportunity to decline to participate in the study and not undergo the WBCT without any loss of benefits to which the participant was otherwise entitled.
3. Potential Risk: Surgery and surgical device implantation risks including infection and foreign body reactions or sensitivities. Other specific adverse effects noted for the study devices include: osteomyelitis surrounding the TightRope, failure of the implant resulting in re-diastasis, and painful aseptic osteolysis related to the wear of the FiberWire (not noted for XP). The InternalBrace does not have any known increased risk beyond potential material sensitivity.
    - Risk Mitigation: All reasonable limitations and protections against potential

adverse health effects that may be associated with surgery and device implantation will be in place:

i. The study doctor will complete standard of care evaluations to determine whether the patient is a good candidate for either of the TightRope fixation procedures.

ii. During the consent process, the research team and the participant will discuss and assess the participant's history and determine if the potential risk of device or surgical related risks are acceptable for that participant. The participant will be given the opportunity to decline to participate in the study and not undergo the TightRope procedure without any loss of benefits to which the participant was otherwise entitled.

iii. Standard of care procedures will be followed during the procedure to minimize the risk of infection and device failure.

iv. Post-operative directives and follow-ups will follow standard of care to minimize device failure, and any adverse effect throughout study timeline will be reported as required and outlined above.

4. Potential Risk: Psychosocial stress or discomfort as a result of filling out the questionnaires

    - Risk Mitigation: All reasonable procedures will be in place to protect against psychosocial stress or discomfort related to questionnaires, and patients will be informed that participation is voluntary and that they may cease participation at any time.

Potential Benefits to Participation

There are no known benefits to the participants for participating in the study. However, it is possible that their involvement may advance knowledge and evidence regarding best practices for caring for ankle injuries that disrupt the syndesmosis.

STATISTICAL ANALYSIS PLAN

Significance will be set a priori at P = 0.05. All statistical analyses will be conducted using IBM SPSS Statistics, Version 28 (IBM Corporation, Armonk, NY). Descriptive analysis will be performed to describe participant characteristics and independent t-tests will be used to determine differences in pre-operative characteristics and outcomes between groups. In order to compare the 3D syndesmotic volume between groups, the volume ratio will first be calculated for each patient by dividing the syndesmotic volume of the contralateral uninjured ankle by the syndesmotic volume of the operative ankle.[11] Separate t-tests will then be performed to determine whether there are differences between the volumetric ratios, FAOS scores, and SF-36 scores between groups at each collection time point. Pearson-product moment correlations will be conducted to explore relationships between the volumetric ratios and each PRO (FAOS and SF-36) at both 6-weeks and 3-months. Pearson correlation coefficients (r) will be interpreted as (negligible < 0.3, low = 0.3-0.49, moderate = 0.5-0.69, high = 0.7-0.89, very high = 0.9-1.0).

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