STATISTICAL ANALYSIS PLAN

Delayed loading following repair of ruptured Achilles tendon – A randomized controlled trial

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Background

Leisure time physical activity is unquestionably associated with numerous health benefits. However, some of these recreational activities are also accompanied with some increased risk of injury. For example, there appears to be an increased risk of Achilles tendon ruptures with some recreational sports (1). Specifically, this increased incidence can be seen in high-impact sports, including badminton, volleyball, and soccer (2, 3). Acute Achilles tendon ruptures occurs in both men and women but is most frequent in men 30-50 years of age that participate in recreational sports periodically (1, 4, 5). The prevalence is reported to be ~ 18 per 100,000 per year, and the incidence appear to be on the rise (1, 4-6). Yet, evidenced based knowledge of how to best rehabilitate the injury after repair of the rupture is largely absent in the literature, which likely contributes to the reports of persistent muscle weakness, tendon elongation and incomplete return to pre-injury level (7-18). It has been suggested that preventing tendon elongation during rehabilitation improves the clinical outcome, which is the very aim of this project.

Purpose

The purpose of the present study is to investigate if delayed loading following surgical treated Achilles tendon rupture influence the clinical outcome and muscle and tendon structure after one year.

Hypotheses

We hypothesize that delaying the gradual introduction of loading in the initial 26 weeks may reduce the heel-rise deficit (primary outcome) and thus improve the clinical outcome one year after surgery (primary endpoint).

Study design

This study is a single-blinded prospective randomized controlled superiority trial with 2 parallel arms. (The study will be registered by ClinicalTrials.gov). We will examine if delaying initiation of loading in the initial 26 weeks will influence the tendon healing and elongation compared to current accepted clinical guidelines for rehabilitation (‘accelerated rehabilitation’) of surgically repaired Achilles tendon ruptures. One arm will include current clinical practice that calls for partial weight bearing from week 3, full weight bearing from week 7, and total bracing time 6

weeks. The other arm will not be allowed partial weight bearing with the use of crutches until week 7 and full weight bearing until week 13, and total bracing time is 12 weeks.

Participants

The patient recruitment will be achieved in-house from the emergency clinic and the orthopedic surgery department at Bispebjerg and Frederiksberg Hospital. Potential participants are either identified by the diagnosing doctor, or by the primary investigator through screening of the orthopedic surgery-lists. Furthermore, features of the SP-journal system will be used to support recruitment. For patients identified by the diagnosing doctor, once the diagnosis of Achilles tendon rupture is established, patients are orally informed about the study and if interested in participating they will receive the written attending information ("Deltagerinformation"). Patients identified through the orthopedic surgery-lists will be approached by the primary investigator in person on the day of surgery and will be given the same oral and written information as those identified by the diagnosing doctor. Patients interested in participating will either contact the primary investigator or will be approached in person on the day of surgery, to be screened for eligibility. The orthopedic surgeons will assess all patients after standard procedures and, if surgical intervention is decided, patients will undergo the standard surgical procedure. After surgery, patients will be randomized to one of the two rehabilitation groups:

A) Early mobilization. This constitutes the currently accepted regime and is therefore considered the control group.

B) Delayed mobilization.

Randomization procedure is performed using a computer-generated block randomization (blocks of 4) procedure.

Blinding

Because this is an "open-label" trial the health professionals delivering the interventions and the participants will not be blinded to treatment allocation. Outcome assessors will be blinded to treatment allocation whenever possible: This is of outmost importance, and participants are requested not to disclose their allocation when outcomes are assessed.

Sample size calculation

Based on heel-rise deficit (primary outcome) relative to the uninjured side (u_A=76 %, u_B=90 %, σ=16) a sample of n=21 is required to detect a difference with a power of 80% (19). To account for drop-outs a sample of 24 in each arm will be recruited.

Outcome assessments

Primary outcome

The primary outcome is heel-rise height deficit on the injured side relative to the uninjured side at one-year follow-up.

Secondary outcomes

The following outcomes are assessed as secondary outcomes:

- Heel-rise work.
- Achilles Tendon Total Rupture Score (ATRS).
- Gastrocnemius and soleus muscle fascicle length and pennation angle.
- Gastrocnemius and soleus tendon and lower limb muscle cross-sectional area.
- Plantarflexion Isokinetic muscle strength.
- Physical actively level (PAS).
- Tendon length.
- Achilles Tendon Resting Angle (ATRA).

Population to be analyzed

To be included in the study, participants must meet the following in- and exclusion criteria:

Inclusion criteria	Exclusion criteria
• Diagnosed with a traumatic, complete mid-substance Achilles tendon rupture • No contraindications for MRI • Presented within 14 days from injury • Adult (18 to 60 years) • Understand Danish • Manage transport to/from the hospital on their own	• Other injuries affecting their lower limb functions • Prior Achilles tendon rupture • Re-rupture • Smoking • Systemic diseases influencing tendon healing • Anticoagulation treatment • Inability to follow rehabilitation or complete follow-ups • Immunosuppressive treatment including systemic corticosteroid treatment.

Intension-to-treat (ITT)

All participants who are randomized.

Per protocol (PP)

All participants who adhere to the major criteria in the protocol and completed the whole study period and attended 1 year follow-up. Participants with missing data on any of the variables in the model will be excluded from the specific analysis at the specific timepoint.

Analysis

All outcomes will be reported using descriptive statistics. Normally distributed data by the mean and standard deviation and skewed distributions by the median and interquartile range. Binary and categorical variables will be presented using counts and percentages. SAS and Prism will be used for all statistical analysis. Analyses in addition to the descriptive statistics are described below.

Primary outcome

The primary analysis will be an assessment of the between group difference in heel-rise height deficit on the injured side relative to the uninjured side ((uninjured-injured/uninjured) x 100)) at one-year follow-up. Intention-to-treat and per-protocol analysis will be conducted. The criteria for being included in the per-protocol analysis is having attended 1 year follow-up tests. An unpaired students t-test will be used to analyze the primary outcome (heel-rise deficit) at the primary endpoint (one year).

Secondary outcome

A mixed model (group x time) that includes all timepoints will be used to analyze the secondary outcomes and the primary outcome. In addition, a correlation matrix for the changes in secondary and primary outcome will be performed, followed by a multiple regression. ATRA will be compared with MRI and correlated.

Table of the analysis

OUTCOME	TIMEPOINTS	UNPAIRED T-TEST	MIXED MODEL	CORRELATION	MULTIPLE REGRESSION
MRI Tendon length CSA tendon CSA muscle Free fat fraction	4		x	x	x
ULTRASOUND Fascicle length Pennation angle Thickness muscle Doppler tendon Thickness tendon	4		x	x	x
HEELRISE Work Hight Repetitions	2		x	x	x
ATRA	2		x	x	x
MUSCLE STRENGTH	1	x		x	x
ATRS	2	x		x	x
PAS	2	x		x	x
LIKERT SCALE	1	x			

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