STATISTICAL ANALYSIS PLAN

Early progressive resistance strength exercise for treatment of acute Achilles tendon rupture. A randomized controlled trial

Study group
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1. Study Synopsis

Regardless of choice of either surgical or non-surgical treatment for Achilles tendon ruptures, there is known long-term muscular deficits and a decreased function after Achilles tendon rupture(1,2). Early functional rehabilitation (EFR) during the first eight weeks of treatment is a multimodal strategy with elements ranging from weight-bearing to more specific exercises intended to load the Achilles tendon. Generally, the design of the intervention protocols in the available literature are very heterogeneus and the contents of EFR varies considerably(3,4), and few studies has examined the effect of strengthening exercises(5–7). We performed a feasibility study where early progressive resistance exercises showed high acceptability by the patients and the compliance with the exercises were high. The aim of this study is to investigate the efficacy of standard care versus standard care combined with early progressive resistance exercises in improving the Achilles tendon Total Rupture Score (ATRS) 13 weeks after non-surgical treated Achilles tendon rupture.

2. Study Objectives, Hypothesis and Outcomes

2.1. Primary Objective and Outcome

The primary objective is to investigate the efficacy of standard care versus standard care combined with an early exercise program in improving the ATRS (8,9) 13 weeks after non-surgical treated Achilles tendon rupture.
We hypothesize that individuals with Achilles Tendon rupture randomized to standard care with early exercises will have a significantly higher ATRS score after 13 weeks (primary endpoint) compared to individuals receiving standard care only.

The primary outcome ATRS is a validated self-reported questionnaire for acute Achilles tendon rupture. It consists of 10 items concerning limitations related to symptoms and physical function. Each item is rated from 0 (very limited function) to 10 (not at all limited). Items: strength, fatigue, stiffness, pain, activities of daily living, walking on uneven surfaces, walking quickly upstairs or uphill, running, jumping and hard physical labour. The ATRS is validated in a Danish population(9) and is used in the Danish Achilles Database DADB(10).

2.2. Secondary Objectives and Outcomes

The secondary objectives are to compare the secondary outcomes between standard care versus standard care combined with an early exercise program. In long-term follow-up to compare changes from 13 weeks follow-up to 26 and 52-weeks follow-up between groups. The objective outcomes are measured for injured and un-injured side and also presented as a side to side difference.
The outcomes are:

1. ATRS at 26- and 52 weeks

2. Physical Activity Questionnaire (IPAQ)(11) short form Danish version. It consists of 7 items concerning physical activity and gives an estimate of the total weekly physical activity measured in MET-minutes per week. The questionnaire will be filled out at 13-, 26- and 52-weeks follow-up.
3. Fear of re-rupture is measured by The Tampa scale of Kinesiophobia (TSK) (12). The questionnaire consists of 17 items concerning pain and kinesiophobia and has 4 answers from "Strongly disagree" to "Strongly agree" with a total range of 17 to 68 points. Four questions are reversed. Measured at baseline and at 9-, 13- and 52-weeks.
4. Fear of loading the Achilles tendon. Dichotomous Yes/no
    a. During exercises. Measured at 9-weeks.
    b. After weaning of the walking boot. Measured at 13 weeks
5. Percentage of the patients that can perform a one-legged heel-rise at 13- and 52 weeks.
6. Muscle endurance is measured with the MuscleLab measurement system (Ergotest Technology, Oslo, Norway)(13). Presented in Joules and repetitions.
    a. Seated heel-rise test at 13 weeks*. External weight load on the knee is calculated to 30% of the bodyweight.
    b. One-legged standing heel-rise test at 52-weeks.
7. One-legged heel-rise height(13). Presented in centimeters.
8. Isometric muscle strength. Measured as maximal isometric plantar flexor muscle strength using Fysiometer(14). Position: seated with 90 degrees flexion in hip and knee. Measured at 9, 13, 52 weeks.
9. Achilles tendon resting angle (ATRA) is validated as an indirect measure of the Achilles tendon length (15).
10. Achilles tendon length in centimeters. Copenhagen Achilles length measure (CALM) using ultrasound(16). Performed at 9, 13 weeks and 52weeks.
11. Serious adverse events: Re-rupture, non-union, deep vein thrombosis (DVT).
12. Compliance with exercises. Number of sessions.
13. Cost-effectiveness outcomes. Self-reported health state as measured by the EQ-5D-5L(17). Work productivity outcomes are measured using the Work Productivity and Activity Impairment Questionnaire WPAI:GH (18) and condition-related expenses as measured by a self-developed questionnaire. Measured at 9, 13, 26, 52 weeks.

* Measures of strength endurance is different at the shortterm follow-up 13-weeks and 52-weeks as the standing one-legged heel-rise is not possible to perform for all patients in the early phase(13).

2.3. Descriptive Outcomes

Descriptive data will be registered at baseline: age, sex, height, weight, body mass, pre-injury work and physical activity status (ATRS, IPAQ, WPAI:GH), cause of injury, health status.

2.4. Specification of endpoints

The primary outcome ATRS will be measured at the primary endpoint 13 weeks.

3. Study Design

This study is designed as a randomised controlled superiority trial.

3.1. Sample Size

Sample size calculations is based on the primary endpoint ATRS with a clinical relevant difference at 10 points and estimated standard deviation 15 point(19,20). With a two-sided 5% significance level and a power of 80%, the sample size will be 37 in each group and a total of 82 patients when allowing for potential dropouts.

3.2. Randomization and Blinding

The randomization procedure:

The participants will be allocated to two groups in a 1:1 randomization using a computer-generated sequence on www.sealedenvelope.com. A staff member with no connection to the project will be responsible for generation of the randomization key and numbered sealed opaque envelopes.

The randomization will be Permuted Block Randomization in block sizes of 2, 4 and 6 with stratification for hospital allocation to allow for minor differences in the treatment (the intervention will be the exact same at the two places, but there could be minor differences in treatment procedure) due to different logistic/culture at the two hospitals. As there is a male to female ratio of 3-5:1 sex is also added to the stratification.

Blinding procedure:

The participants and the physiotherapist supervising the exercise sessions cannot be blinded. The physiotherapist performing the outcome assessment at follow-up will be blinded to the group allocation. The assessor will not be involved in the intervention or be affiliated with the treatment sites. Participants are asked to keep the group allocation secret from assessor. The principal investigator and the statistician performing the statistical analysis will be blinded.

4. Study Population

Study participants will be included after the first visit to the emergency departments at Aalborg University Hospital and at North Denmark Regional Hospital Hjørring.

Inclusion criteria:

- Acute Achilles tendon rupture treated non-surgically.
- Diagnosed within 3 days of injury.
- Age 18-65 years and able and willing to participate in the intervention
- Able to speak and understand Danish.

Exclusion criteria:

- Achilles tendon rupture close to insertion on calcaneus or in the musculo-tendinous junction of the triceps surae.

- Previous Achilles tendon rupture or other conditions in either leg causing lower leg disability (pain, deficits in strength or range of movement).
- Treated with fluorquinolons or corticosteroids within the last 6 months.
- Diabetes or rheumatic diseases.
- Severe medical illness: ASA score higher than or equal to 3 (21).

Excluded patients and patients not willing to participate will follow the usual program of rehabilitation for non-surgical treatment at Aalborg University Hospital. They can participate in a separate cohort with the questionnaires at the same follow-up time points.

5. Data handling

The data will be collected and stored in RedCap at Aalborg University Hospital. There will be a separate entry form in RedCap with questionnaires for the participants. A link to the questionnaires will be sent by email, and for follow-up it will also be available from a computer at each session.

6. Statistical Analysis

The data analysis will be performed using the latest STATA version.

Information on screening, randomization and completing follow-up will be presented in a CONSORT flow diagram.

6.1. Primary Endpoint

Descriptive statistics (mean (standard deviation) or median (interquartile range) for continuous variable or frequencies and proportions for categorical variables) will be used to describe demographics, for the two treatment groups individually and overall sample.

The primary intention-to-treat analysis will investigate the between-group difference in ATRS. We will use a linear mixed effects regression model with the participant as random effect and time 13, 26 and 52 weeks, group allocation (standard care vs standard care plus add-on) and baseline value as fixed effects. Conclusions will only be drawn based on the primary endpoint (13 weeks). We will use Q-Q plots and histograms to assess data normality.

6.2. Secondary Endpoints

Will be presented with descriptive statistics as above.

6.3. Major Protocol Deviations

Any protocol deviations that happen during the course of the study will be registered.

6.4. Missing data

All data will be analyzed as intention to treat. In case of mis-diagnostics that is discovered after randomization, the participant will be excluded from the study.

6.5. Exclusion cohort

Will be reported descriptively.

7. Implementation of Analysis Plan

This statistical analysis plan is a supplementary to the study protocol and will serve as a working document for the statistical analysis. All data is registered in REDCap and exported to a secure research file system at Aalborg University Hospital for analysis and storage.

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