Statistical Analysis Plan of GhenTendon trial

Section 1: Administrative Information

Title:

Effectiveness of Reducing Tendon Compression in the Treatment of Insertional Achilles Tendinopathy

The study has been approved by the ethics committee of the University Hospital Ghent (ID: BC-11818) and the study protocol has been registered on ClinicalTrial.gov (ID: NCT05456620). The statistical analysis plan follows the guidelines for the Content of Statistical Analysis Plans in Clinical Trials.[1]

SAP version and date: Version 1, 02/03/23
NCT number: NCT05456620
SAP timing: prepared prior data collection completion

Section 2: Introduction

Background and objectives:

Achilles tendinopathy is a debilitating injury that is common among athletes, especially those involved in running sports. Around 30% of all runners exhibit Achilles tendinopathy with an annual incidence of 7-9%. Of these patients, roughly one-third will have insertional Achilles tendinopathy (IAT). Several mechanisms are considered to play a role in the etiology of Achilles tendinopathy, yet a prominent role seems present for excessive overload. Traditionally, the nature of this overload is thought to be purely tensile. However, the Achilles tendon can also be exposed to compressive loads at the insertion when the tendon wraps around the posterior prominence of the calcaneus during dorsiflexion of the ankle. The formation of fibrocartilage-like tissue, which is typically found in histological examination of tendinopathy, can be considered as an adaptation to this compressive load, driven by the tenocyte's mechanotransduction process. Therefore, it is recommended to reduce the amount of compressive load on the tendon during rehabilitation while exerting sufficient tensile load. However, these recommendations are mainly based on a pilot study and expert opinion. Therefore, this RCT investigates the effectiveness of low tendon compression rehabilitation (LTCR) with high tendon compression rehabilitation (HTCR) in recreational athletes with IAT. Limiting the amount of tendon compression on the Achilles tendon insertion will be achieved by (1) patient education, (2) heel inserts and (3) an adapted exercise regimen. The specific objectives of this RCT are to investigate whether LTCR results in better outcomes then HTCR in terms of Achilles tendon pain, function and structure.

Section 3: Study Methods

Trial design:

- Superiority trial
- Randomized controlled parallel group design
- Assessor blinded
- Single-center

Randomization:

Randomization will be performed after baseline assessment. Patients will be randomized in a 1:1 ratio to receive either LTCR (interventional) or HTCR (control) treatment. We will use a permuted block randomization technique with a variety in block sizes, in order to reduce potential allocation prediction and to achieve balance in allocations of patients to the intervention and control arm, stratified according to the preinjury activity level of the patients, for which we used the Cincinnati Sports Activity Scale (CSAS) (level 1 or level 2), and tendon pain severity, for which we used the Victorian Institute of Sports Assessment-Achilles (VISA-A) score (<50 or ≥50 points).

Sample size:
A sample size calculation was conducted a priori based on the primary outcome measure, the VISA-A score. To detect a clinically significant mean difference of 10 points in the VISA-A score, with 90% power and a standard deviation of 8.4, and with an alpha level of 0.05, a total of 40 participants would be required. This calculation also accounts for a 20% dropout rate.

Statistical interim analyses:
No interim analysis for safety, nor for futility and efficacy will be conducted.

Timing of final analysis:
All outcomes will be analyzed in August 2024

Timing of outcome assessments:
The data will be collected by the researchers at baseline (i.e. T0), 12 weeks post-baseline (i.e. T1), and 24 weeks post-baseline (i.e. T2).

Section 4: Statistical Principles

Confidence intervals and P values:
All applicable statistical tests will be performed using a 5% significance level. All confidence intervals presented will be 95% to indicate the precision of the estimates in this RCT.

Intervention adherence:
Exercise adherence will be assessed weekly by recording the days patients performed exercises during the preceding week. Global adherence will be calculated as the percentage of completed daily exercises out of the prescribed daily exercises.

Analysis populations:
The RCT data will be analysed according to the 'intention-to-treat' principle. This means that ppatients will be analyzed according to allocated treatment, regardless of any intercurrent event that may occur after randomization.

Section 5: Trial population

Eligibility:
The inclusion criteria for patients (all criteria are connected by 'AND'):

1. Aged 18-60 years
2. Performing running-based sports (≥ 2 times/week)
3. Clinically and ultrasonographically confirmed chronic IAT
4. Experiencing Achilles tendon symptoms for more than 3 months but less than 3 years
5. Severity level of less than 80 points on the VISA-A score

The inclusion criteria for patients:

1. A history of Achilles tendon rupture or surgery
2. Coexisting mid-portion Achilles tendinopathy or ankle pathology
3. Other treatment with physiotherapy, local injection, extracorporeal shockwave or orthotics in the past 3 months
4. Presence of metabolic, endocrine or rheumatological disorders
5. Use of fluoroquinolone therapy in the preceding 2 years
6. Pregnancy

Recruitment:
The CONSORT flow diagram will be used to summarize the number of patients who were assessed for eligibility, approached, consented, randomized and received their allocated treatment. We will also provide reasons for not approaching patients, and reasons of patients who refused to participate.

Withdrawal/Follow-up:
We will present data for each follow-up time point on withdrawal and lost to follow-up in the CONSORT flow diagram with numbers and reasons for withdrawal and number included in the analysis.

Baseline patient characteristics:
The characteristics of the patients and family carers will be described in terms of age, gender, BMI, training hours per week, duration of complaints, smoking, pathological side, presence of Haglund deformity of calcifications. Baseline patient characteristics will be summarized, both for the control group and the intervention group. The mean and standard deviation or absolute and relative frequencies will be given for the descriptive variables. For these variables, t-tests or Mann-Whitney U tests will be performed for assessing differences between randomized groups on these baseline variables.

Section 6: Analysis

Hypothesis primary endpoint:
The LTCR intervention is expected to result in better outcomes in terms of Achilles tendon pain, function, and structure in recreational athletes with IAT compared to the HTCR intervention.

Primary endpoint and measure:
Primary endpoint is mean difference in score on the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire at 12 and 24 weeks between LTCR and HTCR. This validated, reliable, self-administered patient-reported outcome evaluates Achilles tendon pain, function, and ability to play sports. The maximum score is 100, with a lower score indicating greater clinical severity.

Secondary endpoints and measures:
The secondary endpoints were mean difference at 12 and 24 weeks in:

- Patient satisfaction, which is categorized as excellent, good, moderate, or poor.
- Return to sports rate, which is categorized as return to desired sports at pre-injury level; return to desired sports but not at pre-injury level; return to sports but not the desired sports; and no return to sports.
- Visual analogue scale (0-100 mm) for pain during daily activities over the past 7 days
- Visual analogue scale (0-100 mm) for pain during 10 unilateral hops
- Score on the lower extremity functional scale questionnaire. Total score ranges from 0 to 80, where a higher score indicating better lower limb function.
- Score on Tampa scale for kinesiophobia questionnaire. Total score ranges from 17 to 68, where the lowest 17 means no kinesiophobia.
- Score on the EQ-5D-5L questionnaire. Total score ranges from -0.59 to 1, where 1 is the best possible health state.
- Achilles tendon insertion anteroposterior diameter, assessed by ultrasonography in longitudinal view (5 mm distal from the posterosuperior calcaneal border).
- Achilles tendon insertion doppler signal (modified Ohberg Scale; 0-4), assessed by ultrasonography.
- Heel-rise endurance test
- Exercise adherence rate

Analysis methods:
We will explore the data graphically by means of histograms and QQ plot. We will test for differences in mean score at T1 and T2 for the primary and secondary outcomes between the intervention and control groups. Linear mixed-model analyses with a random intercept model will be used for the continuous variables, with treatment, time, and treatment-by-time interaction as independent variables. Additionally, adjustments for potential baseline covariates including age, gender, BMI, symptom duration, CSAS, VISA-A, and presence of an associated Haglund's deformity and/or retrocalcaneal bursitis will be made. Estimated marginal means with corresponding 95% CI will be reported at baseline and follow-up, both for the intervention and control group. Moreover, the estimated mean difference between the LTCR and HTCR group at T1 and T2 will be reported with 95% CI. Relationships between categorical variables will be analyzed using Fisher's exact test. Patient satisfaction was dichotomized into satisfied (excellent/good) and dissatisfied (moderate/poor). Return to sport was dichotomized into return to the desired sport and no return to desired sport. Differences in exercise adherence between the intervention and control groups will be assessed by a t-test.

Missing data:
We will not use a multiple imputation method because we assume that the missingness of the outcome data is not random. Instead, it likely depends on the difference in effectiveness between the LTCR and HTCR interventions and is therefore related to the true outcome values. Consequently, we will conduct post hoc sensitivity analyses for the primary endpoint using worst-case and best-case scenarios to assess the robustness of our findings.[2] For participants who dropped out, VISA-A scores from the last observation will be carried forward. Additionally, in the worst-case scenario (favoring the control group), missing values will be replaced by the group mean + 2 SD in the HTCR group, and the group mean - 2 SD in the LTCR group at both time point. In the best-case scenario (favoring the interventional group), this approach will be reversed.

Intercurrent events:
In line with the 'intention-to-treat' principle, we will disregard intercurrent events, such as treatment discontinuation, during analysis.

Statistical software:
Data will be analysed by using IBM SPSS version 28 or more recent.

References:

1. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-2343. doi:10.1001/JAMA.2017.18556
2. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - A practical guide with flowcharts. BMC Med Res Methodol. 2017;17(1):1-10.