Study protocol and statistical analysis plan

The Ultrasound-Monitored Changes in Achilles Tendinopathy After Focused Extracorporeal Shock Wave Therapy - a Randomized Sham-Controlled Trial

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Study design and description

This work is designed as a randomized, sham-controlled clinical trial in which we monitor the effects of low-energetic focused shock wave therapy (ESWT) on Achilles (AT) tendinopathy. We estimate that at least 18 patients will participate in it. They will be randomly divided into two groups in 1:1 ratio. Group A will receive ESWT according to selected parameters (see below). Group B will receive placebo in the means of sham-ESWT (see below).

Patients in both groups will have same program. The research within one patient will last in total of 8 weeks from the initial to the end examination. In the initial week the patient will be clinically examined by a physiotherapist, an ultrasonography (USG) examination will be performed and VISA-A questionnaire will be filled. At the end of this session, the patient will be randomly assigned to group A or B and receive first application (ESWT or sham-ESWT). For the next 4 weeks, once a week, the next applications will be performed. The interval between individual applications should be at least 5 days. Thus, a total of 5 applications of ESWT or sham-ESWT will be performed. The final examination will be performed at 3 weeks follow up after the last application and includes the same procedures as in the initial examination.

Patient selection

Patients will be included in the study if they meet these inclusion criteria:

- the patient complains about Achilles tendon pain, which limits (at least partially) his quality of life during daily activities or sport, and this condition could be referred as a tendinopathy
- the patient's other leg is asymptomatic
- the patient is not aware of the symptomatical mechanical tendon damage in past (eg. partial or complete rupture due to injury)
- the patient has no previous experience with ESWT

Patients will not be included if:

- the patient has condition which is contraindication for ESWT
- the patient has symptomatical mechanical tendon damage in past (eg. partial or complete rupture due to injury)
- the patient has previous experience with ESWT

Patients distribution and randomization

Patients will be randomly divided into two groups (Group A, Group B) in a 1:1 ratio. Patients in Group A will receive low-energetic focused ESWT according to selected parameters. Patients in Group B will receive placebo (sham-ESWT). The patients themselves will not know which group they are in. Before, during, and even after the session, patients will not be allowed to see the applicator or machine. The sham applicator will have to be always pepared before the patient come into the intervention room.

Due to the fact that AT tendinopathy includes a wider range of causes that can be monitored by USG examination, the finding on USG examination will also be taken into account when dividing into groups. In each group the specific cause should be represented in similar proportion. For this reason, the patient will be assigned to one of the groups only after the initial examination.

Initial and final examination

During the initial and final examinations, the several tasks to the patient will be performed. Firstly the anamnestic data will be collected, then the ankle dorsiflexion range of motion will be measured using the “weight-bearing lunge test” (cm). Thompson's test and resistance test will be

performed at the same time. The area of greatest pain will be localized by palpation. Then patient will also perform AT loading tests on both legs — single leg heel rise test and single leg hop test. The patient will perform as many heel rises/hops using only one leg as possible in 30 seconds or until first sign of pain in Achilles tendon area. This will be also measured in asymptomatic leg.

Secondly, the patient will be asked to complete a validated Victorian Institute of Sports Assessment - Achilles questionnaire, which assesses the subjectively perceived severity of the disease and partly its impact on the quality of normal daily or sports activities.

The patient's maximal pain will be assessed using a standardized numerical rating scale (NRS) of pain. The patient will be asked about the maximum pain that could be caused by various factors, at the initial examination, at the last application and during the final examination.

Lastly, the ultrasonographic examination of patient's AT in both legs will be performed. This examination is described in the following chapter.

Both, inital and final examinations in each patient will be performed by only one person (the investigator of the study) and the same person will prepare and perform each application of ESWT or sham-ESWT.

Ultrasonographic examination

USG examination will be performed with a Mindray DC-70 machine with a linear probe type L12-3E with a frequency of 12 Hz in the preset "MSK" mode. The whole area of AT will be monitored from the connection of soleus fibers to the insertion site on the calcaneus by longitudinal and transverse imaging.

The echotexture and continuity of the tendon, the echotexture of KFP, the presence of RC bursa, calcifications and osteophytes will be evaluated visually. At the same time, the possible degree of vascularization in or around the tendon will be evaluated using Doppler mode.

The values of anteroposterior tendon width, paratenon thickness, and CSA at the anteroposterior widest point will be collected using the measuring instruments included in USG machine.

USG findings will be consulted and evaluated in cooperation with an expert in USG diagnostics to increase their relevance and reduce the error rate.

ESWT application

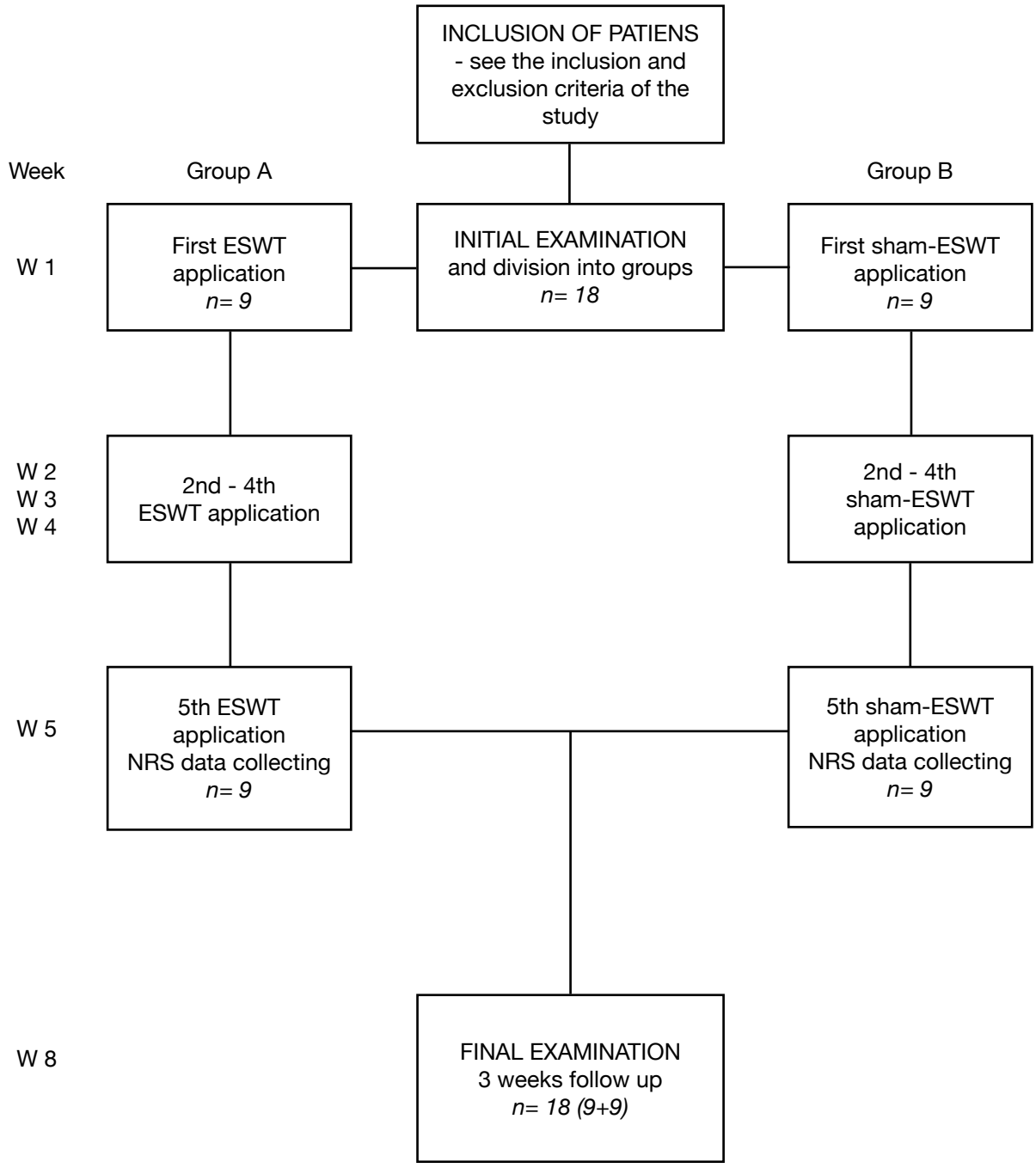
The focused ESWT will be applied to patients in Group A from the BTL-6000 FSWT device with a penetration depth modulating len for the treatment of superficial structures. Energy Flux Density will be set in the low-mid energy spectrum to 0.12 mJ / mm2, frequency 10 Hz, with a total number of shocks of 1300. The application will be performed semi-statically using an USG gel in the area of the largest USG finding. Of the total numbers of shocks, 500 shocks will be applied from both sides of the AT, then 300 shocks from the dorsal side of the tendon will be applied as well. The set values will not change throughout the study.

Sham applicator

Sham-ESWT will be performed to patients in Group B from the same machine. Sham-ESWT is the application of ESWT with a specially modified applicator that does not allow the penetration of shock waves into the tissue. A 3-4 cm thick pulp (air filled material) covered with medical latex material will be placed over the applicator. The modification is self-made, based on the knowledge of physical principles of ESWT.

The set intensity, frequency, total number of shocks and form of application will be the same as in group A, so the audio stimulus from the strength of the generated wave, the duration of application and sensitive sensations of skin movement will be similar in both groups. No side or therapeutic effects are expected with the applicator modified in this way.

Graphically represented study design:



Data analysis

In this study, the comparison of the results in groups A and B in the final examination compared with the baseline values will be evaluated.

Firstly, descriptive statistics (mean, median, standard deviation, minimum and maximum) of the initial and final values in both groups will be performed. Normal data distribution will be determined by the calculated Shapiro-Wilk p-value.

Then, a two-way ANOVA tests will be used to evaluate the statistical significance of effects comparison in both groups for most of the measured parameters (not including the tendon loading tests). Also the Tukey method will be performed to determine effects of each part of ANOVA testing.

In addition, paired t-tests or the Wilcoxon test will be performed for each group of each parameter. Thus, the statistical significance of the changes in the most of the parameters for each group will be calculated.

The number of repetitions in Achilles tendon loading tests (single leg heel rise / hop test) will only be analyzed by descriptive statistics to see the indicative change in results. There will also be collected a number of those patients who describe the pain during these tests.