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The proximal hamstring avulsion clinical trial (PHACT)—a randomised controlled non-inferiority trial of operative versus non-operative treatment of proximal hamstrings avulsions: study protocol

Elsa Pihl,[1] Målfrid Holen Kristoffersen,[2] Anne-Mari Rosenlund,[3] Sofia Laszlo,[4] Mida Berglöf,[1] Eva Ribom,[4] Karl Eriksson,[5,6] Frede Frihagen,[3] Ville M Mattila,[7] Jörg Schilcher,[8,9] Martin Eklund,[10] Greta Snellman,[4] Mikael Skorpil,[11] Olof Sköldenberg,[6] Carl Johan Hedbeck,[1] Kenneth Jonsson[4]

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For numbered affiliations see end of article.

Correspondence to
Dr Elsa Pihl; elsa.pihl@ki.se

ABSTRACT

Introduction The treatment of proximal hamstring avulsions is controversial. While several trials have investigated the outcome for patients treated surgically, there is today no prospective trial comparing operative treatment with non-operative treatment. This protocol describes the design for the proximal hamstring avulsion clinical trial (PHACT)—the first randomised controlled trial of operative versus non-operative treatment for proximal hamstring avulsions.

Methods and analysis PHACT is a multicentre randomised controlled trial conducted across Sweden, Norway and Finland. Eligible patients (60 participants/treatment arm) with a proximal hamstring avulsion of at least two of three tendons will be randomised to either operative or non-operative treatment. Participants allocated to surgery will undergo reinsertion of the tendons with suture anchors. The rehabilitation programme will be the same for both treatment groups. When patient or surgeon equipoise for treatment alternatives cannot be reached and randomisation therefore is not possible, patients will be invited to participate in a parallel observational non-randomised cohort. The primary outcome will be the patient-reported outcome measure Perth hamstring assessment tool at 24 months. Secondary outcomes include the Lower Extremity Functional Score, physical performance and muscle strength tests, patient satisfaction and MR imaging. Data analysis will be blinded and intention-to-treat analysis will be preformed.

Ethics and dissemination Ethical approval has been granted by the Ethical Committee of Uppsala University (DNR: 2017–170) and by the Norwegian ethical board (REC: 2017/1911). The study will be conducted in agreement with the Helsinki declaration. The findings will be disseminated in peer-reviewed publications.

Trial registration number NCT03311997

Strengths and limitations of this study

- This is the first randomised clinical trial on operative versus non-operative treatment of proximal hamstring avulsions.
- The multicentre design will support external validity and implementation.
- The treatment outcome will be assessed with a hamstring-specific validated Patient Related Outcome Measure (PROM), objective functional tests and imaging.
- Owing to the type of interventions, blinding of the patients and treatment providers is not possible.

INTRODUCTION

The treatment of proximal hamstring avulsions is controversial. The literature suggests that surgical treatment is the treatment of choice. For example, in a recent systematic review by Bodendorfer *et al*,[1] it is claimed that surgically treated patients have better results in psychometric scores, functional and strength tests than non-surgically treated patients. However, existing literature may be biased. The studies conducted so far are mainly retrospective case series[1 2] and have only occasionally used validated outcome measures, such as Harris Hip Score[3] and Lower Extremity Functional Scale (LEFS).[3–5] The Perth hamstring assessment tool (PHAT)[6] is designed and validated for follow-up of patients with hamstring avulsion,[6] but was only recently developed.

Bodendorfer *et al*[1] only found 28 non-surgical-treated patients compared with 767 surgical-treated patients to include in their review, suggesting a publication bias in the existing literature and providing limited power for comparisons between the surgically and non-surgically treated patients. In the light of the apparent lack of comparative studies, one needs to be aware of surgical

complication rates when suggesting operative treatment. With a reported aggregated complication rate as high as 23% in the surgically treated group,[1] surgery cannot be considered harmless.

The aim of this prospective, multicentre, randomised controlled trial is to provide reliable evidence on how to treat physically active patients, 30–70 years of age, with proximal hamstring avulsions. We will use PHAT[6] at 24 months post-treatment allocation as our primary outcome measure.

METHODS AND ANALYSIS

Study design and setting

The proximal hamstring avulsion clinical trial is a multicentre, prospective, preference-tolerant, randomised, controlled, non-inferiority trial with two treatment arms. The protocol was developed in accordance with Standard Protocol Items: Recommendations for Interventional Trials and Template for Intervention Description and Replication statements.[7 8]

The study is conducted in cooperation with Swedish Orthopaedic Trauma Society and has 11 study sites at orthopaedic departments across Sweden, Norway and Finland. Inclusion started in September 2017 and recruitment is expected to finalise in 2021, which would allow for read-out of the primary endpoint in 2023.

Recruitment strategy

Patients with proximal hamstring avulsions that are diagnosed or referred to the orthopaedic department at 1 of the 11 hospitals will be screened for participation in the study. Eligible patients are invited to participate and provided with oral and written information. Thereafter, patients are asked to sign a written informed consent statement before any study procedure occurs.

Patients

Inclusion criteria

Patients must fulfil all the inclusion criteria and must not have any exclusion criteria to be eligible for randomisation.

1. Age at injury between 30 and 70 years.
2. Physical examination supports the diagnosis; for example, a positive hip extension test, palpable defect and/or local tenderness and haematoma.
3. MRI shows a complete acute avulsion of at least two of three tendons from the footprint at the ischial tuberosity.
4. Patient has a moderate to high activity level.
5. Patient has linguistic and mental ability to understand the rehabilitation programme explained in Swedish, Norwegian, Finnish or English.
6. Time from injury to inclusion in study is <4 weeks.

Exclusion criteria

1. Diabetes with secondary complications.
2. Previous major lower extremity injury or disease with sequelae.
3. Moderate or severe liver, pulmonary, kidney, psychiatric or heart disease that significantly increases the risk of complications after operative treatment.
4. Severe obesity (Body Mass Index, BMI >35).
5. Alcohol or substance abuse.
6. High energy injury or combinations of injuries affecting the lower extremity.

Intervention

We will randomly assign patients to either operative treatment (n=60) with suture anchor reinsertion of the tendons to the footprint at the ischial tuberosity or to non-operative treatment (n=60). Both groups will follow the same standardised rehabilitation protocol.

To minimise bias by indication, we will offer the patients who are eligible but where patient or doctor equipoise to treatment cannot be reached to participate in a parallel follow-up cohort with identical treatment options and follow-up. In the parallel cohort, the patients/surgeons preferred treatment is provided.

Surgical procedure

Patients allocated to the operative group will undergo surgery at the earliest convenient time but no later than 6 weeks after the injury. The surgeon may choose whether to make a longitudinal or transversal skin incision. The proximal ends of the avulsed tendons are identified and after dissection they are reattached to the ischial tuberosity using at least two suture anchors. Data on the surgical approach, the number of suture anchors and their manufacturer as well as the surgeon's intraoperative assessment of retraction and the number of tendons invovlved will be collected.

Rehabilitation

The rehabilitation protocol is based on a previously published rehabilitation protocol[9] and will be the same for both treatment allocations. In brief, no brace is used. Full weight bearing is allowed. The patients are instructed to keep their stride length short, and to avoid sitting and any motion that stretches the hamstring for the first 3 weeks. Patients are instructed to perform isometric exercises of the quadriceps and gluteal muscles to avoid muscle atrophy. After 2 weeks, isometric contractions of the hamstring muscles are allowed and progressed with cautious dynamic exercises during week 4. Specific hamstring strengthening exercises are begun after 5 weeks.

Study outcomes

Primary outcome

The primary outcome measure will be the patient-reported PHAT score[6] at 24 months. PHAT is a condition-specific questionnaire with maximum score 100, with a higher score corresponding to higher function. The questionnaire uses a visual analogue scale for pain scores during different activities, as well as categorical scores for activity levels and tenderness, and has been shown to be sensitive to clinical changes.[10]

Secondary outcomes

Additional patient-reported outcomes

The LEFS[11] will be used to assess patient-reported outcome. LEFS is a reliable, valid and responsive tool for assessing functional status in several populations with lower extremity musculoskeletal conditions.[11 12] Information regarding physical activity level will be collected using the short form of International Physical Activity Questionnaire.[13 14] Furthermore, data on general satisfaction, return to work and return to sports will be collected.

Functional tests and muscle strength tests

The functional performance will be assessed through the timed step test,[15] which is a test previously validated for knee arthroplasty patients and the single leg hop test, which is a performance-based test validated in anterior cruciate ligament trials.[16] Measurement of maximum kinetic force (Newton, N) will be conducted using a handheld isometric dynamometer (microFET 2; Hoggan health industries).[17] Study sites equipped with a computer-based isokinetic dynamometer, Biodex,[18 19] will assess peak torque (N) and total workload (Joule, J) of the hamstrings. All strength and functional performance tests will be reported with ratio of injured/uninjured leg, with the uninjured leg serving as reference for each subject.

Imaging outcomes

MRI will be used at 24 months to evaluate the entire thigh muscle volume and to assess muscle and tendon quality. We will use the uninjured side as reference for each subject.

Data collection procedure

At inclusion demographic data activity at injury and time from injury to treatment is collected. Follow-up visits are planned at 3, 6, 12 and 24 months. A study nurse will provide a set of questionnaires for the patients to fill out. The nurse will also scan the patients' charts for adverse events or complications. A physiotherapist that is blinded to the intervention will perform the strength and functional test at 6, 12 and 24 months. At the 24-month follow-up, MRI of both thighs will be performed.

Sample size

Taking into account the cost and risks associated with surgery, and the fact that the literature clearly recommends surgery, a non-inferiority design was considered appropriate. Thus, the study aims to demonstrate that non-operative treatment is no worse than operative treatment by more than the non-inferiority margin.

Based on the existing literature the SD of PHAT measurements is ~16–21.[6 20] A reasonable non-inferiority margin is half of the SD and this effect size is lower than the minimal detectable change of the PHAT.[6] To achieve 85% power, with α=0.5, for demonstrating non-inferiority using a non-inferiority margin of 10, 50 patients in each arm are required. Heterogeneity of treatment effects is likely in surgical interventions and is best handled by increasing power. Some crossover and loss to follow-up will occur. For these reasons, we will continue inclusion until at least 60 patients in each group has initiated treatment.

Randomisation procedure

The REDCap (REDCap Software) randomisation tool will be used to facilitate randomisation.[21] Allocation tables with a random block size (2-6), stratified by study site, were created by a statistician and uploaded blinded into the REDCap project. The randomisation is permanent and not editable within the participant record and, like all other activity within REDCap, is tracked and not modifiable in the audit log.

Blinding

To minimise ascertainment bias this trial is single-blinded, where the physiotherapist conducting strength and functional tests at 6, 12 and 24 months will be blinded to the intervention, by informing the patients not to tell and asking them to wear clothes concealing the surgery scar. The statistician analysing the data will also be blinded to treatment arms.

Data management

All study data will be collected and managed in a digital case report form using REDCap electronic data capture tools hosted at Karolinska Institutet. REDCap is a secure, web-based application supporting data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.[21]

Data will be kept securely in order to protect confidentiality before, during and after the trial. A codebook matching the personal identification number and the trial identification number is kept at each study site and the trial identification number is noted in the patient's electronic chart. The study nurses and investigators can log on and enter data directly into the database. Patients will complete surveys at each visit. Any paper forms used are stored for cross-checking at each study site.

Statistical analysis plan

The flow of patients through the trial is displayed in a Consolidated Standards of Reporting Trials diagram (figure 1). The number of patients screened for trial entry; those who are ineligible and the reasons why; number of eligible patients not providing consent; and the number of eligible patients subsequently randomised will be presented. The characteristics of the screened population, the ineligible participants and eligible participants who consent and do not consent will be summarised. Information regarding the number of surgeons and centres, as well as number of patients treated by each surgeon will be provided. Data on patient eligibility and reasons for withdrawal from treatment or the trial will be summarised. Baseline patient characteristics will be summarised using

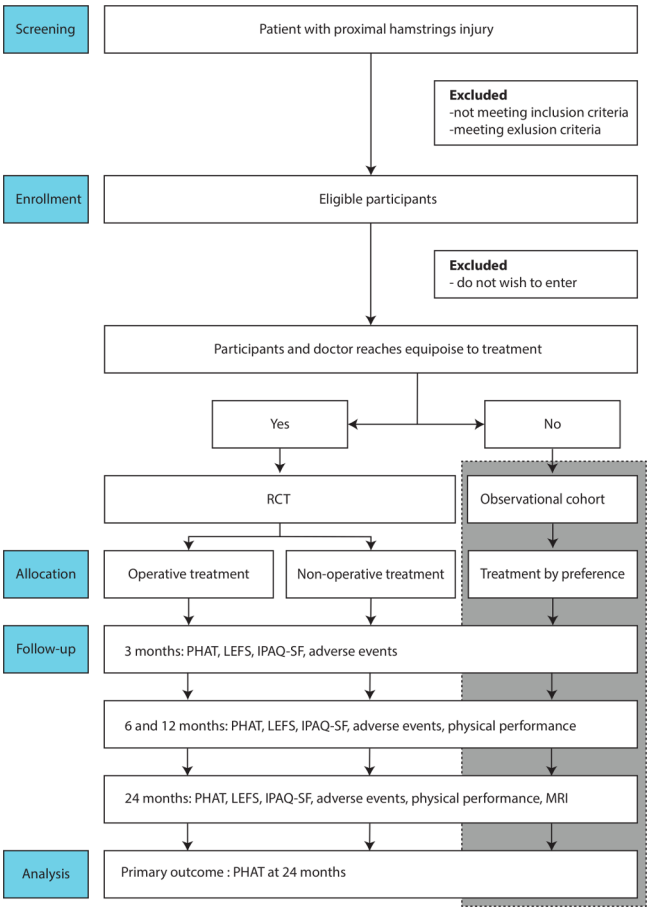

Figure 1 Flowchart. This study illustrates the study design. IPAQ-SF, short form of International Physical Activity Questionnaire; LEFS, Lower Extremity Functional Scale; PHAT, Perth hamstring assessment tool. RCT, Randomised Controled Trial.

descriptive statistics; counts for categorical variables and mean/median and IQR for continuous variables.

Primary analyses will be by intention-to-treat (ITT). However, since ITT analyses can be anti-conservative for non-inferiority trials, we will also conduct perprotocol and as-treated analyses. Cases will only be considered treatment crossovers if the randomly assigned treatment is changed by patient preferences. Non-operative treated patients who are treated operatively due to late complaints (>3 months after inclusion) will not be considered crossovers.

All analyses will be conducted blinded for treatment allocation. All statistical tests will be two-sided with an α of 0.05. Differences between groups in continuous skewed main outcome variables will be analysed by the Mann-Whitney U-test, and by the t-test when variables are from a symmetrical distribution. Results will be presented with 95% CIs. Two-way-tables with the χ^2 test will be used for dichotomous variables. No adjustment of p values for multiple comparisons (secondary analyses) will be undertaken.

In secondary analyses, multivariate regression models will be used to analyse the primary outcome (PHAT score at 24-month follow-up). The main variables of interest included are the intervention, age, sex, study site and the degree of tendon retraction. We will also jointly analyse all timepoints in a linear mixed model (to adjust for within-patient correlations). Patients will be treated as a random effects, and time points, randomisation arm, age at baseline, sex and degree of tendon retraction will be included as fixed effects. As further secondary analyses, the randomised and observational cohorts will be analysed together using propensity scores adjustment (the randomised patients will get propensity score 0.5). The propensity score will be based on age, sex, study site, IPAQ and the degree of tendon retraction.

We will test for heterogeneity of treatment effects by testing for significant interactions in the following subgroups: tendon retraction >2 versus ≤2 cm and age >50 versus ≤50 years.

Missing data can occur in two different ways in the study: (1) questions in the PHAT questionnaire can be left unanswered and (2) patients can miss specific follow-up visits or drop out of the study altogether. Missing PHAT score questions will be imputed based on the answered questions. Missed follow-up visit at 24 months will be handled using a multiple imputed model for the primary analysis. The multiple imputation protocol will be based on a longitudinal model for predicting PHAT at 24 months based on the PHAT score recorded at previous time points together with patient age, sex and degree of tendon retraction. The mixed-effects model handles data missing at random seamlessly and no imputation will be needed for that specific analysis. We will test the robustness of the results to data not missing at random by assuming a missingness model where missingness is associated with PHAT score.

Adverse events and complications

At follow-up, questions with the aim of identifying adverse events and serious adverse events will be provided. Medical records will also be checked for adverse effects. Undesired events such as surgical site infections, neurological sequelae, thromboembolism, rerupture or failure and hypertrophic scarring in surgical patients are defined as adverse effects. Serious adverse effects are defined as events resulting in death, hospitalisation or threatening life, that is, pulmonary embolism, sepsis or cardiovascular complications.

Patient and public involvement

Patients were not formally involved in designing the study protocol. In the process of designing the study protocol and selecting the primary outcome, a few patients were interviewed in clinical practice. Patients have been invited to participate in monitor meeting with researchers from the participating sites present. The participants will receive a written summary of main findings when the study is finished.

Ethics and dissemination

The study will be conducted in agreement with the Helsinki declaration.

As both treatment options are accepted in the catchment area for the study, the randomisation procedure was deemed ethically acceptable. The results will provide evidence-based treatment algorithms for future patients.

The primary study results will be submitted for publication to an international, peer-reviewed journal, regardless of whether the results are positive, negative or inconclusive in relation to the study hypothesis.

Author affiliations
[1]Karolinska Institutet Danderyds Sjukhus, Karolinska Institutet, Stockholm, Sweden
[2]Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway
[3]Division of Orthopaedic Surgery, Oslo University Hospital, Oslo, Norway
[4]Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden
[5]Department of Clinical Science and Education Södersjukhuset, Karolinska Institute, Stockholm, Sweden
[6]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden
[7]Department of Orthopeadics, Tampere University Hospital, Tampere, Finland, Tampere, Finland
[8]Department of Orthopeadic Surgery, Linköping University Hospital, Linkoping, Sweden
[9]Department of Clinical and Experimental Medicine, Linköping University Hospital, Linköping, Sweden
[10]Karolinska Institutet, Stockholm, Sweden
[11]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Collaborators The PHACT collaborative study group consists of all local investigators who are responsible for the execution of the trial and valid data gathering. They have all read and approved the final manuscript.

Contributors All authors have contributed to the design of this trial protocol. EP, CJH and KJ have initiated the project. KJ is the primary investigator. The protocol was drafted by EP and KJ and was refined by MHK, A-MR, MB, ER, KE, FF, GS, JS, ME, VMM, MS, OS and CJH. Statistical advice was provided by ME. MB and ER designed the protocol for physical functional tests and the rehabilitation program. MS, EP and SL developed protocol for the imaging outcomes. SL was responsible for drafting the manuscript. All authors have read and approved the final manuscript.

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Competing interests Nothing to declare

Patient consent for publication Written informed patients consent will be collected in the PHACT-study.

Ethics approval Ethical approval has been granted by the Ethical Committee of Uppsala University (DNR: 2017–170) and the Norwegian Regional Ethical Committee (REC: 2017/1911).

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REFERENCES

1. Bodendorfer BM, Curley AJ, Kotler JA, *et al*. Outcomes after operative and Nonoperative treatment of proximal hamstring Avulsions: a systematic review and meta-analysis. *Am J Sports Med* 2017;363546517732526.
2. van der Made AD, Wieldraaijer T, Kerkhoffs GM, *et al*. The hamstring muscle complex. *Knee Surgery, Sports Traumatology, Arthroscopy* 2015;23:2115–22.
3. Chahal J, Bush-Joseph CA, Chow A, *et al*. Clinical and magnetic resonance imaging outcomes after surgical repair of complete proximal hamstring ruptures. *Am J Sports Med* 2012;40:2325–30.
4. Hofmann KJ, Paggi A, Connors D, *et al*. Complete avulsion of the proximal hamstring insertion: functional outcomes after nonsurgical treatment. *J Bone Joint Surg Am* 2014;96:1022–5.
5. Skaara HE, Moksnes H, Frihagen F, *et al*. Self-Reported and performance-based functional outcomes after surgical repair of proximal hamstring avulsions. *Am J Sports Med* 2013;41:2577–84.
6. Blakeney WG, Zilko SR, Edmonston SJ, *et al*. Proximal hamstring tendon avulsion surgery: evaluation of the Perth hamstring assessment tool. *Knee Surgery, Sports Traumatology, Arthroscopy* 2017;25:1936–42.
7. Hoffmann TC, Glasziou PP, Boutron I, *et al*. Better Reporting of Interventions: Template for Intervention Description and Replication (TIDieR) Checklist and Guide]. *Gesundheitswesen* 2016;78:e174.
8. Chan AW, Tetzlaff JM, Altman DG, *et al*. Spirit 2013 statement: defining standard protocol items for clinical trials. *Rev Panam Salud Publica* 2015;38:506–14.
9. Askling CM, Koulouris G, Saartok T, *et al*. Total proximal hamstring ruptures: clinical and MRI aspects including guidelines for postoperative rehabilitation. *Knee Surgery, Sports Traumatology, Arthroscopy* 2013;21:515–33.
10. Blakeney WG, Zilko SR, Edmonston SJ, *et al*. A prospective evaluation of proximal hamstring tendon avulsions: improved functional outcomes following surgical repair. *Knee Surgery, Sports Traumatology, Arthroscopy* 2017;25:1943–50.
11. Binkley JM, Stratford PW, Lott SA, *et al*. The lower extremity functional scale (LEFS): scale development, measurement properties, and clinical application. North American orthopaedic rehabilitation research network. *Physical therapy* 1999;79:371–83.
12. Mehta SP, Fulton A, Quach C, *et al*. Measurement properties of the lower extremity functional scale: a systematic review. *J Orthop Sports Phys Ther* 2016;46:200–16.
13. Craig CL, Marshall AL, Sjostrom M, *et al*. International physical activity questionnaire: 12-country reliability and validity. *Medicine & Science in Sports & Exercise* 2003;35:1381–95.
14. Lee PH, Macfarlane DJ, Lam TH, *et al*. Validity of the International physical activity questionnaire short form (IPAQ-SF): a systematic review. *International Journal of Behavioral Nutrition and Physical Activity* 2011;8.
15. Marmon AR, McClelland JA, Stevens-Lapsley J, *et al*. Single-Step test for unilateral limb ability following total knee arthroplasty. *J Orthop Sports Phys Ther* 2013;43:66–73.
16. Reid A, Birmingham TB, Stratford PW, *et al*. Hop testing provides a reliable and valid outcome measure during rehabilitation after anterior cruciate ligament reconstruction. *Phys Ther* 2007;87:337–49.
17. Reurink G, Goudswaard GJ, Moen MH, *et al*. Strength measurements in acute hamstring injuries: Intertester reliability and prognostic value of handheld dynamometry. *J Orthop Sports Phys Ther* 2016;46:689–96.
18. Drouin JM, Valovich-mcLeod TC, Shultz SJ, *et al*. Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. *Eur J Appl Physiol* 2004;91:22–9.
19. Pincivero D, Lephart S, Karunakara R. Reliability and precision of isokinetic strength and muscular endurance for the quadriceps and Hamstrings. *Int J Sports Med* 1997;18:113–7.
20. Best R, Eberle J, Beck F, *et al*. Surgical Refixation after Proximal Hamstring Tendon Avulsion Injuries: Does the Time of Surgery Influence Functional Outcomes?]. *Sportverletzung Sportschaden : Organ der Gesellschaft fur Orthopadisch-Traumatologische Sportmedizin* 2017;31:160–6.
21. Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.