STATISTICAL ANALYSIS PLAN (SAP)

Physical activity after periacetabular osteotomy followed by progressive resistance training or progressive resistance training alone for hip dysplasia: secondary analysis of the randomized controlled PreserveHip trial

Trial ID: PreserveHip

Trial registration: ClinicalTrials.gov, NCT03941171

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INTRODUCTION

Background

Hip dysplasia is characterised by insufficient acetabular coverage of the femoral head, leading to altered hip biomechanics and increased joint contact pressure (1-4). The condition is associated with hip pain, impaired function, and reduced physical activity, as well as an increased risk of hip osteoarthritis (5-9). Periacetabular osteotomy (PAO) is the standard surgical treatment, while non-surgical management, including progressive resistance training (PRT), has also been proposed as an alternative treatment option (10, 11).

Rationale for this study

The PreserveHip randomised controlled trial found no superiority of PAO followed by PRT compared with PRT alone for improvement in patient-reported hip pain among individuals with hip dysplasia eligible for PAO surgery (12). Previous studies have reported discordance between patient-reported outcomes and objectively measured functional outcomes (9, 13, 14). This secondary analysis was therefore conducted to investigate whether PAO followed by PRT, compared with PRT alone, is associated with differences in objectively measured physical activity one year after initiation of treatment.

Aims

Primary efficacy aim: To compare the objectively measured daily number of steps one year after initiation of treatment between participants randomised to PAO followed by PRT and participants randomised to PRT alone.

Secondary aim: To compare the objectively measured daily number of steps one year after initiation of treatment in participants with hip dysplasia to daily step counts in healthy subjects.

Tertiary aim: To investigate the association between objectively measured daily number of steps and patient-reported hip outcomes one year after initiation of treatment.

STUDY METHODS

Trial design

This study is a secondary analysis of data from the PreserveHip trial, a multicentre randomised controlled trial conducted at Aarhus University Hospital and Odense University Hospital in Denmark and at Oslo University Hospital in Norway. The PreserveHip trial was designed as a parallel-group superiority trial with a 1:1 allocation ratio. Participants were randomly assigned to either PAO followed by usual care and eight months of PRT or 12 months of PRT alone. The present secondary analysis focuses on objectively measured physical activity outcomes assessed one year after initiation of treatment. Analyses comparing the two intervention groups preserve the original randomisation. Comparisons with healthy subjects are observational and non-randomised. We prespecified and registered the PreserveHip

trial at ClinicalTrials.gov (NCT03941171), and we have previously published the trial protocol (15) and the blinded interpretation of the primary results (16). This statistical analysis plan (SAP) is reported in line with the 'Guidelines for the Content of Statistical Analysis Plans in Clinical Trials'(17), while the reporting of this secondary analysis will follow the "Consolidated Standards of Reporting Trials" (CONSORT) statement (18).

Randomization and blinding

After completion of baseline assessments, participants were randomised in a 1:1 ratio to either PAO followed by PRT or PRT alone. Randomisation was performed using a computer-generated allocation sequence implemented in REDCap (19, 20), with permuted blocks of variable size (4, 6, and 8). Allocation concealment was ensured through an external randomisation service provided by the Clinical Trial Unit, Department of Clinical Medicine, Aarhus University, Denmark. Due to the nature of the interventions, participants were not blinded to treatment allocation, whereas outcome assessors performing follow-up assessments were blinded.

Sample size and power considerations

The PreserveHip trial was originally designed and powered for the primary outcome of patient-reported hip pain measured using the Hip disability and Osteoarthritis Outcome Score (HAGOS) (21). Prior to trial initiation, sample size calculations estimated that 48 participants per group would provide 80% power to detect a between-group difference in change from baseline to 12 months of 9.7 points on the HAGOS pain subscale, assuming a standard deviation of 16.2 and allowing for dropouts and crossovers (15). No formal sample size or power calculation was performed for the present secondary analysis of objectively measured physical activity. All analyses will be based on the analysis population defined below. Results from the present analyses will therefore be interpreted with consideration of their exploratory nature.

Statistical interim analyses and stopping guidance

No interim analyses were performed during the PreserveHip trial. Trial enrolment was discontinued before reaching the originally planned sample size due to slow participant recruitment. Trial enrolment and attrition rates were monitored throughout the study.

Timing of final analysis and outcome assessments

Outcome assessments for this secondary analysis of the PreserveHip trial were conducted at two time points: baseline and one year after initiation of the assigned treatment. The timing of the one-year follow-up assessment was defined as 12 months after treatment initiation, irrespective of randomization group. The specific time points for all outcome measurements were prespecified and are described in the published trial protocol (15).

STATISTICAL PRINCIPLES

Confidence intervals and p-values

All statistical tests will be two-sided and 95% confidence intervals (95% CIs) will be reported for all estimated effects. Statistical significance will be evaluated at a nominal significance level of 0.05 ($P < 0.05$) for all outcomes. No formal adjustment for multiple comparisons will be applied.

Analysis populations

The primary analysis will be conducted in a modified intention-to-treat (mITT) population, defined as all randomised participants with valid baseline physical activity measurements. Valid physical activity measurements are defined as at least three valid days with a minimum of 10 hours of accelerometer wear time per day. This criterion is required for inclusion in the statistical analyses and for imputation of the one-year outcome. Randomised participants who do not meet this criterion will be excluded from the analyses. Activity measure from participants included in the mITT population will be analysed according to their originally assigned randomization group, irrespective of treatment adherence or treatment crossover. This population represents the treatment policy estimand and will be used for all analyses comparing participants randomised to PAO followed by PRT with participants randomised to PRT alone.

A sensitivity analysis following the same approach as the primary analysis will be performed based on the complete-case population. The complete-case population is defined as all randomised participants with both valid baseline and follow-up physical activity measurements.

Healthy subjects with valid physical activity measurements meeting the same accelerometer wear-time criteria will be included in a separate observational analysis population. Comparisons involving healthy subjects are non-randomised and exploratory.

TRIAL POPULATION

Eligibility

Screening and recruitment were conducted in accordance with the prespecified eligibility criteria of the PreserveHip trial protocol (15). Participants with hip dysplasia were recruited following referral from primary care to the Departments of Orthopaedics at Aarhus University Hospital and Odense University Hospital in Denmark and Oslo University Hospital in Norway. Eligibility was assessed based on demographic, clinical, and radiographic information, and detailed inclusion and exclusion criteria are described in the published trial protocol (15). Eligible participants were invited to enrol after confirmation of eligibility and provision of written informed consent. Healthy subjects were recruited through networks associated with the PreserveHip trial and through advertisements at Aarhus University, VIA University College, and Aarhus University Hospital. Healthy subjects were aged 18–40 years, had no hip-related symptoms, and fulfilled prespecified criteria for hip function and general health. Screening and recruitment

data, including numbers screened, eligible and enrolled, will be summarised descriptively and reported in a CONSORT flow diagram.

Baseline patient characteristics

Baseline characteristics of randomised participants in the PAO and PRT groups and of healthy subjects will be presented descriptively (Table 1). Continuous variables will be summarised as means with standard deviations or medians with interquartile ranges, and categorical variables as counts and percentages. No statistical testing will be performed to compare baseline characteristics between groups, as baseline tables are intended solely to describe the study population before treatment initiation.

STATISTICAL ANALYSIS

Outcome definitions and endpoints

The primary outcome is the objectively measured daily number of steps at one year after initiation of treatment, assessed using tri-axial accelerometry (AX3, Axivity Ltd., Newcastle, UK) with data post-processed using a custom-designed algorithm implemented in MATLAB (22, 23). The primary endpoint is the between-group difference in the estimated mean daily number of steps at one year between participants randomised to PAO followed by PRT and participants randomised to PRT alone. Baseline number of steps and the site of inclusion will be included as covariates in the statistical model. All physical activity-related outcomes are presented in Table 2. Additionally, the six dimensions of HAGOS will be used to assess patient-reported outcomes (21).

Analysis methods

Primary and secondary physical activity outcomes will be analysed using analysis of covariance (ANCOVA) models. For comparisons between randomised treatment groups, the outcome measured at one year will be modelled with randomization group as the main factor. The corresponding baseline value of the outcome and site of inclusion will be included as covariates to reduce random variation. The primary estimand is the between-group difference at one year, and results will be reported as adjusted mean differences with corresponding two-sided 95% confidence intervals. A sensitivity analysis following the same approach as the primary analysis will be performed based on the complete-case population.

Comparisons involving healthy subjects will be analysed using multiple linear regression with the outcome being activity measured at one year for the two intervention groups and activity measured at baseline for the healthy subjects. The groups will be the main factor and the analysis will be adjusted for age and sex. These comparisons are observational and exploratory.

Associations between objectively measured physical activity outcomes and HAGOS scores will also be analysed using multiple linear regression models, adjusted for age and sex. To assess whether the association between physical activity and HAGOS differs between randomisation groups, an interaction term between physical activity and randomisation group will be included in the model.

Missing data
Inclusion in the analysis requires valid baseline physical activity measurements and participants without baseline physical activity measurements will be excluded from the analysis. Missing outcome data at one year for randomised participants will be handled using multiple imputation for all three aims, under the assumption that data are missing at random. Imputation will be performed using a regression model including baseline physical activity, age, sex, randomization group and site of inclusion as predictors. A total of 1,000 imputed datasets will be generated, and estimates will be combined using Rubin's rules (24). Healthy subjects will be analysed using observed data only. A sensitivity analysis of complete cases (participants with complete follow-up) will be performed for all three aims.

Statistical software
All statistical analyses will be performed using Stata version 19.5 (StataCorp LLC, College Station, TX, USA).

Tables

Table 1. Baseline characteristics of the modified intention-to-treat population and healthy subjects.

	PAO-group n = xx	**PRT-group** n = xx	**Healthy-group** n = xx
Female, n (%)			
Age (years), mean (SD) or median (IQR)			
BMI (kg/m^2), mean (SD) or median (IQR)			
Duration of hip symptoms, n (%)			
None			
0-6 months			
6-12 months			
1-2 years			
2-5 years			
5-10 years			
More than 10 years			
Missing			
Civil status, n (%)			
Married			
Cohabiting			
Single			
Divorced			
Widow/widower			
Not informed			
Educational level, n (%)			
Primary school			
Vocational education			
High school or similar			
Short higher education			
Medium higher education			
Long higher education			
Other education			
Employment status, n (%)			
During education			
In work			
In employment activation, sick leave, available, etc.			
Outside the labour market			
Alcohol consumption, n (%)			
Below 2 items per week			
2-7 items per week			
8-14 items per week			
Above 15 items per week			
Missing			
Smoking behaviour, n (%)			
Never smoked			
Quit smoking			
Sometimes			
Daily			

Outcomes will be presented as means with standard deviation (SD) or medians with interquartile range (IQR) or numbers (n) with proportion (%). PAO = Periacetabular osteotomy. CE-angle = Wibergs centre edge angle. AI-angle = Acetabular Index angle.

Table 2. Physical activity-related outcomes.

Dimension	Outcome	Timeframe	Unit
Frequency			
	Steps	One-year after initiating treatment	Number per day
	Cycling rotations	One-year after initiating treatment	Number per day
Intensity			
	Average cadence	One-year after initiating treatment	Steps per minute
	Very-low intensity activity	One-year after initiating treatment	Percentage per day
	Low intensity activity	One-year after initiating treatment	Percentage per day
	Moderate intensity activity	One-year after initiating treatment	Percentage per day
	High intensity activity	One-year after initiating treatment	Percentage per day
Time			
	Wear time	One-year after initiating treatment	Hours per day
	Walking	One-year after initiating treatment	Hours per day
	Standing	One-year after initiating treatment	Hours per day
	Sedentary	One-year after initiating treatment	Hours per day
	Cycling	One-year after initiating treatment	Minutes per day
Type			
	Sit to stand transfers	One-year after initiating treatment	Number per day
	Short walking bouts	One-year after initiating treatment	Number per day

Table 3. Physical activity per day described by the dimensions of F.I.T.T. measured one year after periacetabular osteotomy (PAO) for the PAO-group and one year after initiation of progressive resistance training (PRT) for the PRT-group.

Outcomes, mean (95% CI)	PAO-group			PRT-group			Adjusted between-group difference[a]	
	Baseline	One-year	Change	Baseline	One-year	Change	One-year	P-value
Frequency								
Steps, n								
Cycling rotations, n								
Intensity								
Average cadence, steps/min								
Very-low intensity activity, %								
Low intensity activity, %								
Moderate intensity activity, %								
High intensity activity, %								
Time								
Wear time, h								
Walking, h								
Standing, h								
Sedentary, h								
Cycling, min								
Type								
Sit to stand transfers, n								
Short walking bouts, n								

Analysis of covariance with multiple imputations for missing data, based on the modified intention-to-treat population. Results presented as mean with 95% confidence intervals (95% CI). [a]Adjusted for the number of steps at baseline and site of inclusion. Abbreviations: F.I.T.T. = frequency, intensity, time and type; H = hours. Min = minutes. N = number. PAO=Periacetabular osteotomy; PRT = Progressive resistance training

Table 4. Physical activity per day described by the dimensions of F.I.T.T. measured one year after periacetabular osteotomy (PAO) for the PAO-group, one year after initiation of progressive resistance training (PRT) for the PRT-group and at baseline for the healthy-group.

Outcomes, mean (95% CI)	**Healthy-group** Crude mean	**Comparison with the PAO-group** Adjusted difference[a]	P-value	**Comparison with the PRT-group** Adjusted difference[a]	P-value
Frequency					
Steps, number					
Cycling rotations, n					
Intensity					
Average cadence, steps/min					
Very low intensity activity, %					
Low intensity activity, %					
Moderate intensity activity, %					
High intensity activity, %					
Time					
Wear time, h					
Walking, h					
Standing, h					
Sedentary, h					
Cycling, min					
Type					
Sit to stand transfers, n					
Short walking bouts, n					

Results are presented as mean with 95% confidence intervals (95% CI). [a]Adjusted for age and sex. Abbreviations: F.I.T.T. = frequency, intensity, time and type; H = hours. Min = minutes. N = number. PAO=Periacetabular osteotomy; PRT = Progressive resistance training

Table 5. Association between number of daily steps and the Copenhagen Hip and Groin Outcome Score (HAGOS)

	Crude analysis		Adjusted analysis		
HAGOS	Steps, β (95% CI)	P	Steps, β (95% CI)	R^2	P
Symptoms					
Pain					
Physical function in daily living					
Physical function in sport and recreation					
Participation in physical activities					
Hip and/or groin-related quality of life					

Analysis adjusted for age and sex. CI: Confidence interval. HAGOS: the Copenhagen Hip and Groin Outcome Score. P: P-value. PAO: Periacetabular osteotomy. PRT: Progressive resistance training. R^2: Coefficient of determination. β: Regression coefficient

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APPENDIX

Table A1. Complete-case analysis of the primary analysis.

Outcomes, mean (95% CI)	PAO-group			PRT-group			Adjusted between-group difference[a]	
	Baseline	One-year	Change	Baseline	One-year	Change	One-year	P-value
Frequency								
Steps, n								
Cycling rotations, n								
Intensity								
Average cadence, steps/min								
Very-low intensity activity, %								
Low intensity activity, %								
Moderate intensity activity, %								
High intensity activity, %								
Time								
Wear time, h								
Walking, h								
Standing, h								
Sedentary, h								
Cycling, min								
Type								
Sit to stand transfers, n								
Short walking bouts, n								

Analysis of covariance based on the complete-case population. Results presented as mean with 95% confidence intervals (95% CI). [a]Adjusted for the number of steps at baseline and site of inclusion.
Abbreviations: F.I.T.T. = frequency, intensity, time and type; H = hours. Min = minutes. N = number. PAO=Periacetabular osteotomy; PRT = Progressive resistance training