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Multicenter Prospective Cohort Study on Current Treatments of Legg-Calvé-Perthes Disease

Texas Scottish Rite Hospital for Children

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1. Introduction and Purpose:

Objective

Legg-Calvé-Perthes disease is a childhood hip disorder which is common enough to be a significant public health problem (affects 1 in 740 boys between ages 0—14), but uncommon enough to have a sufficient number of patients from a single institution to perform a definitive prospective study comparing the results of current treatments. The present study will establish a database of prospectively identified patients with Legg-Calvé-Perthes (LCP) Disease and collect information regarding their presentation, treatment, and outcomes in the course of receiving currently available treatments.

Primary Aim

Compare the outcomes of current treatments in the management of four age groups (ages 1- 6, 6—8, 8—11, >11) of patients with Perthes disease at two- and five-year follow-up and at skeletal maturity (age 14 for girls and age 16 for boys). .

Secondary Aims

To assess whether clearer guidelines of treatment can be developed by studying perfusion MRI scans performed early in the course of the disease (stages Ia, Ib, and IIa).

To study the natural history of children presenting with LCP disease between the ages of 1 and 18 with perfusion of over 50% of the capital femoral epiphysis.

Hypothesis

We anticipate that there will be a difference in outcome among current treatment regimens for Perthes disease.

2. Background:

Purpose

Perthes disease is one of the most controversial conditions in pediatric orthopedics in terms of making treatment decisions. It is commonly said that if one consults 10 different pediatric orthopedic surgeons, one will get 10 different opinions on how to treat a child with Perthes disease. The divergence of opinion among pediatric orthopedic surgeons stems from a lack of objective evidence to direct them on what is the best treatment for different age groups of patients with the disease. Current options of treatment for Perthes disease range from non-

operative to operative management [1]. Non-operative options include non-weight bearing, bracing, physiotherapy or exercises, and symptomatic treatments (NSAIDs, activity modification, short-term non-weight-bearing or rest). Operative options include femoral or pelvic osteotomy, shelf acetabuloplasty, arthrodiastasis, core decompression or multiple epiphyseal drilling. While many forms of treatments are being used in clinical practice, current state of knowledge regarding the best treatment and the best time to intervene remains unclear. There is clearly a need to design and perform multicenter prospective studies to determine the outcomes following current treatments for Perthes disease to see if one form of treatment is superior to another for different age groups of patients.

While many clinical studies have been published on Perthes disease, many of these studies suffer from small sample size and research design weaknesses, such as retrospective study design, having inclusion or exclusion bias, and not having enough power to reach conclusive results. Thus, many studies themselves are controversial and inconclusive. In order to carry out better and more definitive studies, it is imperative to have a large group of pediatric orthopedic surgeons with interest and expertise in performing clinical studies in a prospective fashion. The collaborative multi-center team approach will provide a larger patient number and combine resources and expertise to tackle this challenging condition.

3. Concise Summary of Project:

Study Design

Approximately 50 pediatric orthopaedic surgeons from pediatric centers in the US and other countries have agreed to participate in this database as members of the International Perthes Study Group (IPSG). TSRH will be the lead center. Those who agree to participate will seek IRB approval from their own institutions. Data will be collected prospectively and entered into REDCap (Research Electronic Data Capture), a browser-based research database. Patient Reported Outcomes Measurement Information System (PROMIS) questionnaires will be completed via an online testing system, the NIH funded Assessment Center.

1-6 Cohort:
For the 1-6 age patient group, patients presenting in an early stage of the disease (stage I or IIa), the surgeons who treat patients with one of the following treatment regimens currently used in practice will be asked to participate in the study.

1. Non-operative management (i.e., no osteotomy but can include soft tissue release)
2. Operative containment treatment (femoral or pelvic osteotomy or Shelf acetabuloplasty).

6-8 Cohort:
For the 6—8 age patient group, patients presenting in an early stage of the disease (stage I or IIa), the surgeons who treat their patients with one of the following three treatment regimens currently used in practice will be asked to participate in the study [2-4].

1. Non-operative management (i.e., no osteotomy but can include soft tissue release);
2. Operative containment treatment (femoral or pelvic osteotomy or Shelf acetabuloplasty).

8-11 Cohort:
For the 8—11 patient age group, patients presenting in an early stage of the disease (stage I or IIa), the surgeons who treat their patients with one of the following treatment regiments currently used in practice will be asked to participate in the study:

1. Non-operative management (i.e., no osteotomy);
2. Operative containment treatment (femoral or pelvic osteotomy or Shelf acetabuloplasty) followed by 6 weeks of postoperative non-weight bearing; and,
3. Operative containment treatment (femoral or pelvic osteotomy or Shelf acetabuloplasty) followed by 6 months of postoperative non-weight bearing.

>11 Cohort Registry:
For the >11 patient age group, patients presenting in an early stage of the disease (stage I or IIa) we will collect prospective data from surgeons who are currently treating their patients with one of the following alternative treatment regimens [5,6]:

1. Non-operative management (i.e. no osteotomy);
2. Core decompression or multiple epiphyseal drilling of the necrotic femoral head with post-operative non-weight bearing; or,
3. Core decompression or multiple epiphyseal drilling of the necrotic femoral head with application of hinged hip distractor.

Patients who present to an IPSG member or their group during the late stages of the disease (stage IIb or stage III) will also be arranged into four separate age cohorts, identical to the list above. We will collect prospective data from surgeons who are currently treating these patients with operative or non-operative treatment regimens.

Regardless of the patient's stage at enrollment, the patient's age at diagnosis or assigned cohort, the following data will be collected: information regarding patient characteristics at presentation, physical exam findings, responses to Perthes patient and/or outcomes questionnaires, and results of radiographic and MR imaging. Participants will be assigned a unique study number. A secure web application, REDCap, will be used to capture and store research information including de-identified radiographic and MR images, clinical information, and Perthes patient and/or outcomes questionnaire responses.

SUB-STUDY #1 – Patient Reported Outcomes Measurement Information System (PROMIS) Assessment:

PROMIS is a computerized adaptive testing (CAT) tool developed through NIH initiatives to measure the health related quality of life (HRQoL) in adults and children with various diseases. [1] This project will investigate the validity of the Patient Reported Outcomes Measurement Information System (PROMIS) in pediatric patients with Legg-Calve-Perthes Disease (LCPD) in order to establish this instrument as a reliable patient-reported outcomes measure in this population. Once validated, PROMIS will be used to evaluate the quality of life of patients in early and late stages of LCPD. This will identify the effect of disease severity on quality of life in this population, and will aid with identification of areas where treatment advances are most necessary to improve their quality of life.

The purpose of this study is to determine if the PROMIS questionnaire is able to reliably quantitate the health-related quality of life in patients with LCPD. This study will also determine whether or not patients with severe LCPD (based on their x-rays) have decreased health-related quality of life.

All patients willing to complete the PROMIS questionnaires will do so regardless of group, treatment, or stage of the disease. The administration of the instrument is facilitated by the use of an online testing platform, the NIH-funded Assessment Center. Data will be transmitted and stored on a secure and dedicated server for the purpose of this study.

SUB-STUDY #2 – TRANSPHYSEAL NECK HEAD TUNNELING AND DRILLING

This sub-cohort is designed to assess the outcomes of LCP patients treated with surgical containment via multiple epiphyseal drilling or core decompression. All patients enrolled into this sub-cohort will meet inclusion criteria and outcome will be assessed by standard of care procedures identical to the patient's respective age cohort. Data collected will include clinical, radiographic, surgical and patient reported outcomes.

Maximum Number of Local Study Participants: 300

Total Number of Study Participants From All Centers: 1500
Milestones: We anticipate that it will take three years to recruit the target sample size for each age group. Following the recruitment period, it will take up to another twelve years for the final clinical and radiographic follow-up at 5 years and skeletal maturity.

Study Duration: This study will be longitudinal. Initial study duration is fifteen years (3 years for recruitment and up to 12 years follow-up, depending on the child's age of skeletal maturity).

4. Study Procedures:

Description of Study Procedures

The present study will establish a database of prospectively identified patients with Perthes disease meeting study inclusion criteria. Information will be collected regarding their history and clinical findings at presentation, treatment, and outcomes in the course of receiving usual standard-of-care treatment and follow-up. All imaging, such as X-rays and MRIs, are

performed as part of clinical practice and the treatment rendered is also based on the surgeon's current practice.

At two-year follow-up, radiographic parameters will be measured. The parameters will include epiphyseal height, diameter, deformity index, lateral extrusion of the epiphysis, femoral neck diameter and length, and distance between the medial wall of the acetabulum and the medial aspect of the femoral head [7,8].

At five-year follow-up, radiographic parameters will also be measured. The parameters will include a modified Stulberg radiographic classification, epiphyseal height and diameter, femoral head sphericity (application of circles of Mose) and deformity index [9-12].

At skeletal maturity follow-up (age 14 for girls and 16 for boys), radiographic parameters will also be measured. The parameters will include a modified Stulberg radiographic classification, epiphyseal height and diameter, femoral head sphericity and deformity index [9-12].

We will also administer functional outcome questionnaires, the Iowa Hip Score and the modified Harris Hip Score (mHHS), which are measures that evaluate hip function prior to and following surgery.

5. Sub-Study Procedures:

This survey will be administered to a child for a self-assessment if he or she is aged 8 years or older. If the child is between the ages of 1 to 8 years, the questionnaire will be given to the legal guardian and the child to complete as a proxy assessment.

As the PROMIS questionnaires are administered online, patients will be provided with a secure URL linking them to the instrument at the Assessment Center testing platform as well as confidential Study ID to access their questionnaires. They will be provided these details upon enrollment into the study. The time needed to complete these questionnaires is approximately 15-20 minutes. The PROMIS questionnaires can be administered electronically during the provider visit for those patients who prefer to complete the questionnaire during their clinic visit or have limited access to the internet at home. Patients will have the option to complete the assessment with a study investigator present if clarification and explanation regarding certain aspects of the questionnaire is required. Alternatively, participants may complete the instrument from any computer with internet access. Patients who do not complete the PROMIS questionnaire during their visit will be given a paper with the necessary URL, Study ID, and instructions in order to access the questionnaire from another site. Patients who choose this option will be contacted by their provider two weeks after their visit if they have not yet completed the questionnaire online, in order to address any questions or difficulties that may have occurred while trying to access or complete the questionnaire.

Once the patient has completed the questionnaire, a member of the research team will access the patient's clinical and radiographic information from that visit. This information will be used to determine the stage of disease at the time of survey. The patient's demographic information will also be accessed.

Because PROMIS is available only in the English language, this sub-study will include only English-speaking individuals.

6. Criteria for Inclusion of Subjects:

Health status: Patients with Legg-Calvé-Perthes disease (also called juvenile idiopathic femoral head osteonecrosis) are eligible for this study. Since idiopathic femoral head osteonecrosis is relatively uncommon in the >11-year-old age group, we will also include secondary femoral head osteonecrosis cases due to trauma and corticosteroid therapy in the >11-year-old age group.

Age: Patients with Legg-Calvé-Perthes disease between the ages of 1 to 18 years old at the time of first presentation to TSRHC Orthopaedic Clinics are eligible to be enrolled in this study. Patients in the >11-year-old age, who have secondary femoral head osteonecrosis due to trauma and corticosteroid therapy, are eligible to be enrolled in the study.

Gender/race/ethnicity: No particular race, ethnic group, or gender is targeted or excluded from this research.

Ability to speak and read English: Study participants should be able to speak and read English or Spanish. The English consent form and HIPAA Authorization will be translated into Spanish for Spanish-speaking-only study participants. Spanish-speaking translators will be available during the consent process.

Ability to give informed consent: Informed consent is required from the parent(s) or legal guardian(s) of a minor under the age of 18 year old. Written assent is required from study participants between the ages of 10 years old through 17 years old.

7. Criteria for Exclusion of Subjects:

Patients with previous surgical treatment on the affected hip, who otherwise meet the inclusion criteria, will be excluded from enrollment in this study.

8. Sources of Research Material:

The sources of research material will be the study participant's clinical and surgical data, and results of radiographic and pre-/post-operative MR imaging studies. Existing records will be used in addition to information collected as part of the standard of care for this patient population, including the following information:

- Age/DOB
- Gender
- Ethnicity
- Height/weight/BMI
- Birth weight
- Date of first TSRHC Orthopaedic Clinic visit
- Dates of contrast-enhanced MRIs
- Clinical data
- Surgical data
- Family history

- Date of first symptoms
- Date of diagnosis
- Date of radiographic studies
- Age at skeletal maturity
- Results of contrast enhanced MR imaging
- Quality of Life questionnaires (PROMIS, mHHS, Iowa Hip Score)
- History of household smoking
- Concomitant illnesses or disorders
- History of corticosteroid therapy
- History of trauma
- Results of radiographic studies

9. Recruitment Methods and Consenting Process:

Methods

Potential study participants meeting the inclusion criteria will be recruited from the Texas Scottish Rite Hospital for Children Orthopaedic Clinics. They will be patients of the treating orthopaedic surgeon. The surgeon will inform the patient and parent(s) or legal guardian(s) at the time of routine clinic visit that a study is being conducted to determine outcomes of current treatments for patients with Perthes disease, and offer them an opportunity to receive more information about participating in the prospective cohort study.

The surgeon will inform the patient and parent(s) or legal guardian(s) that participation or non-participation will not influence treatment options. The surgeon will not be directly involved in the consent process. The research coordinator will offer the patient and parent(s) or legal guardian(s) the opportunity to take materials with them for further review prior to consenting.

Consenting Process

Patients and parent(s) or legal guardian(s) interested in participating will be referred to a research coordinator for invitation and informed consent. The research coordinator will conduct the consent interview. The research coordinator will review the protocol and consent documents with the patient and parent(s) or legal guardian(s) and give them an opportunity to ask questions. If they choose to participate, they will be allowed to give consent at that time or take the materials for review.

Parent(s) or legal guardian(s) of the patient will provide consent or permission. A child age 10 to17 will provide his or her written assent. The person obtaining informed consent will record documentation of the recruitment process, invitation to participate in the study, and informed consent on a consent checklist form. This completed form will be kept in study files.

If the patient and parent(s) or legal guardian(s) are Spanish-speaking only, consent forms and HIPAA authorizations translated into Spanish will be provided. A Spanish translator will be available during the consenting process.

10. Potential Risks:

Physical Risks: There are no direct physical risks to patients as a result of participation in the study. Radiographic and MR imaging studies will be conducted only for standard of care and not solely for research. The Radiology Department will follow standard shielding protocols during each radiographic examination. Females will be required to complete and sign the TSRHC Radiology Department's "Pregnancy Screening for Radiological Procedures" form prior to their radiographic evaluation. The patients will be exposed to the risks inherent in the treating physicians' usual clinical practices only.

Privacy Risks: There is a risk of violation of patient privacy encountered at each patient visit and data input, but steps will be taken to mitigate this risk. Prior to entering data into the research database, the patient will be assigned a study identifier (code) that replaces his/her name and medical record number. A secure web application, REDCap, will be used to capture and store research information including de-identified radiographic and MR imaging studies, clinical information, and Perthes patient and/or outcomes questionnaire responses. The database server will be maintained behind a firewall at the Texas Scottish Rite Hospital for Children. No study information other than documentation of consent and HIPAA Authorization will be stored on site in electronic or hard copy form.

Special Precautions: Patient data will be collected and analyzed and will be treated with professional standards.

11. Subject Safety and Data Monitoring:

IRB-approved research staff will record data. Primary investigator or research coordinator will verify accuracy of data by visual verification and/or outside audit. Research Coordinator and/or TSRHC Research Advisory Panel (RAP) will verify that procedures are being conducted per the approved protocol. Research Coordinator and/or TSRHC RAP will conduct periodic assessments and monitor changes to protocol, target accrual, and enrollment summary. Study will be reviewed annually at time of continuing review (administrative/regulatory documents, subject files, and database). The TSRHC Research Advisory Panel (RAP) functions as the data and safety monitoring committee.

12. Procedures to Maintain Confidentiality:

All normally used means for protecting participant confidentiality will be strictly adhered to in the following ways:

- Discussions regarding potential research participation will be held in clinic with the usual privacy protection measures, including closing exam room doors and not discussing identifiable patient information in hallways.
- All documentation will be maintained within a limited-access area, available only to individuals involved in the study. Collected data will be maintained by an authorized member of the study team. All data will be kept in locked files and/or password protected electronic files, and will be used for research purposes only.
- No patient information will be disclosed outside the study team.

- Patient identifiers will be retained through completion of study, at which time direct linkages to patient identifiers will be destroyed by shredding the document or by deleting electronic files.
- Data gathered by computer will be submitted through a secure server via a password protected website. Participant information and data forms will be assigned study identification numbers. The data will be stored on a secured server that is accessible only from password protected computers located in a locked research-only office. Only those approved on this protocol will have access this information. At no time will any identifiable information be shared with any outside agencies, institutions, individuals or other entities.
- At no time will any published information identify a participant by name or identification number.

All funding agencies, Institutional Review Boards of involved centers, and the U.S. Department of Health and Human Services will have the right to inspect all medical records related to this study for the purpose of verifying data and patient confidentiality. All requirements for HIPAA compliance concerning patient confidentiality will be adhered to.

13. Potential Benefits:

Legg-Calvé-Perthes disease remains one of the most controversial and challenging conditions to treat in pediatric orthopaedics. It is the most common form of childhood femoral head osteonecrosis, affecting 1 in 740 boys and 1 in 3700 girls [13]. While there are many treatment options available ranging from non-operative to operative treatments, it is unclear which treatment is better for different age groups of patients with Perthes disease.
This multicenter prospective cohort study will provide valuable prospective data on the outcomes of common treatments that are being used.

There are no direct benefits to the study participants. As results will be published, others in society with idiopathic femoral head osteonecrosis or secondary femoral head osteonecrosis may benefit from the knowledge gained from this study. New information may lead to improvements in medical care and treatments. The benefit to the University and investigators is in the form of public recognition and knowledge gained.

14. Biostatistics:

Sample Size Estimation: The sample size for this study was determined based on the decision that the primary outcome for each age group will be a quantitative estimate of the sphericity of the femoral head as a measure of femoral head deformity. A more deformed head will be less spherical.

The sample size for each age group was computed to detect a mean deformity index difference of 10% between the groups (non-osteotomy, early surgical containment treatment, and delayed surgical containment treatment groups) as being statistically significant with 80% power and at 5% level of significance. From data of earlier studies, we have determined that the standard deviation of deformity index was 17 units. The 'a' was corrected for allowing multiple comparison (three-group comparison).

The obtained sample size was 55 subjects in each group. Since the final duration of the study is five years, an anticipated 15% loss to follow-up requires that we need 65 subjects in each treatment group.

($n = 2(Z_\alpha + Z_\beta)^2 \sigma^2 / \Delta^2$ *The 'n master' program was used for the computation of sample size*)

Statistical Analysis Plan: The baseline characteristics will be summarized using appropriate summary statistics. Continuous variables will be expressed in terms of means and standard deviations, and categorical variables will be summarized in terms of frequency and percentages.

Since the primary outcome variable is a continuous variable, it will be checked for normality, and if it satisfies normality assumptions, the t-test will be used for comparison. If the measure fails to satisfy the assumptions of normality, non-parametric methods would be used for the analysis. The results will be expressed in terms of means and its 95% confidence intervals. Categorical secondary outcomes will be compared using chi-square test.

Since there is a scope for follow-up measurements at repeated time points, repeated measure analysis of variance will be employed as a secondary analysis plan. In case a covariate is found to be significant, it will be adjusted for using regression methods in the final analysis.

Additionally, since our goal in using PROMIS to assess quality of life at different points across the 2 year treatment duration of Perthes disease, we need to recruit patients that have already received surgery for Perthes and are now returning for follow up to assess their quality of life during recovery. This increases the population of patients that we can recruit from. Furthermore, not all centers involved in this multi-center study have the technology, space, and time available to allow patients to complete PROMIS so they have opted out of participating in this part of the study and other sites, such as TSRH, will need to recruit more patients.

All statistical tests will be performed at an a-level of 0.05.

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