tillægsprotokol 71226 til projekt H-17021841 date16-08-2021

Protocol

Assessment of Guided Growth after Corrective Hip Surgery in Children with Cerebral Palsy by Conventional Xrays - A national multicentre study.

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Place of the project

A national project of Pediatric Orthopedic in CP

Brief Project Deskription

Only a few hospitals in Denmark are a specialized surgical treatment of children with cerebral palsy (CP). Cerebral palsy is the largest inborn neurological disease in children. In Denmark, we closely monitor these children from the early years as bone and joint deformities develop frequently. Especially, hip subluxation or dislocation are monitored systematically, since this is commonly seen in CP children, which leads to gait disturbances, but especially severe pain and decreased function. This has a high occurrence rate of 25-28 % (1). The more severely affected CP children have a higher risk of hip luxation from their early years of life (2). The late consequences of subluxated hips are poor sitting function, deteriorating gait function and secondary hip arthritis (3,4) and corrective surgery is often needed. Corrective osteotomy has traditionally been used to treat hip displacement. This entails surgical rearrangement of the femoral and pelvic bones, and are large surgical procedures affecting the children for a long time after surgery. Moreover, deformity recurrence is seen in 16-22 % of the procedures, most often due to progressing luxation due to the disease, malunion, non-union or pseudoarthrosis (5,6). The high risk of deformity recurrence as a result of osteotomies means that other strategies are needed to improve the surgical outcome in the future. Growth guided hip surgery is such a 'new' procedure. This is based on early intervention and a minimally invasive procedure using a transphyseal screw to change the growth of the hip of the child to grow back into the hip joint over time. This type of procedure has for long been used to correct lower limb deformities especially varus/valgus deformities of the knees but have also recently been applied to correct varus or valgus deformity in the hip of children with cerebral palsy with promising results (21). An earlier Danish prospective intervention study by members of this research group has shown promising results, and for this reason, we aim for a national prospective randomized study, where we include all 5 surgical centres of Denmark.

The purpose of this study is to examine the skeletal growth and development of the bones of the hip joint after corrective guided growth hip surgery with a transphyseal screw for children with CP. This entails radiographical follow up of 2 years with conventional pelvic radiographs. Furthermore, the impact of surgical procedures on the children life will be evaluated using questionnaires on health-related quality of life and monitoring of their pain status.

Background:

CP is a multidimensional neurologic disease that begins in early childhood and continues throughout life. CP has been described since the late 1800s. For many years, hypoxia during birth was considered the main reason for developing CP. However, now it is widely accepted that 90% of the injuries resulting in CP develop before birth - most likely between the 26th and 32nd week (3). The incidence in Denmark is 2:1.000 in live births and has been steady since the 1990s (7).

CP children are a very heterogeneous group regarding the aetiology, disability type and degree. The interruption or change in the general development is affected both on a biological and psychosocial level. The retardation in motoric development is often discovered before the age of 18 months (3). The motor symptoms may also be accompanied by specific or global cognitive problems, communication problems and problems of social interaction. But in contrast to the general perception, mental retardation is only seen in 28 % (8). Spastic CP represents 75% of the patients and is clinically characterized by increased tonus of some muscle groups. This results in spasticity diminished muscle strength and joint contractures and may lead to stagnated or declining gait function and bone deformities. The degree of deformities depends on the severity of the disease (3). In the first 4 years of a CP child's life, hip stability can be jeopardized, especially in severely affected children. Hip luxation progress and is sometimes very swift, and if more than 50% of the femoral head is outside the acetabular joint by radiographical examination, there is a high risk of subluxation or luxation, and large procedures of hip joint osteotomies are needed. The consequences of subluxated hips – if untreated - are poor sitting function, deteriorating gait function and secondary hip arthritis with severe pain to follow when the children become adults (3,9).

Bone deformities in children with CP develop due to abnormal mechanical tension in the muscles. Treatment aims to prevent the progression of these deformities. Nonsurgical treatments have often been initiated by the application of braces or injection of botulinum toxin in high-tension muscles. These methods have been proven not effective, but soft tissue tenotomies are sometimes with effect in the early stages of hip subluxation. If the hip progresses to luxate, then corrective hip joint osteotomies will be performed. However, deformity recurrence is seen in 16-22 % even in these large procedures and complications of malunion, nonunion or pseudoarthrosis are seen (5,6). These large procedures also often have

a painful, long recovery time. Due to these reasons, other strategies are needed to improve the surgical outcome and procedure quality in the future. Growth guided surgery, where the natural growth of the bones is guiding the bones of the hip joint to correct itself and grow back. The strategy of deformity correction is a well-known and seasoned technique for correction of especially varus/valgus deformities of the knees. But has also recently been applied to correct varus or valgus deformity in the hip of children with cerebral palsy with promising results (21). One of the centres has undertaken a pilot study to examine the efficacy of the procedure using RSA with good results (10-18). In the last 5 years, several studies regarding guided growth of the proximal hip have been presented (19-23). The first studies were animal studies, where varisation of the proximal femur was achieved by placing a screw across the proximal epiphysis of the hip (19, 23). The procedure has been evaluated in a control group, where an effect was demonstrated, and no apparent side effect was shown (19). In the study, hemiepiphysiodesis with screw placement eccentrically and inferiorly was performed on lambs. When examining pelvic radiographs over time after surgery, both the articular trochanteric distance (ATD) and neck-shaft angle (NSA) improved significantly in the group, who received the procedure compared to the control group with sham operations (19).

Human studies on guided growth of the proximal hip have been performed recently in patients with developmental dislocation of the Hip (DDH) (20) and cerebral palsy (CP) (21). The children with CP (age 4-10, GMFCS 4-5) had a minimum of 2 years follow up, and showed significant improvements in Reimers index and head shaft angle (HSA). The transphyseal screw was extracted between 1 and 2 years postoperatively to avoid permanent growth arrest. However, radiographical parameters as Reimers index and HSA continued to improve after screw retrieval from the capital physis (growth zone). Moreover, the screw did not alter or affect the capital physis with growth impediment after retrieval, and there were no surgical complications. The outcome of the studies was a significant improvement in the radiographical parameter of HSA, which is known to minimize the risk for later subluxation (20). Conference presentations of EPOS and EPOSNA annual meetings in 2016 and 2017 also demonstrated significant improvement in the NSA during a 5 year follow up in children with CP (GFMCS 4-5) (22). For this reason, we have planned to undertake a comprehensive study evaluating the procedure of guided growth procedure in the hip for children with CP with mild hip subluxation. This is an early intervention, minimal invasive, small procedure with minimal

impact of these vulnerable children life. As mentioned, soft tissue tenotomies are sometimes performed with effect in the early stages of hip subluxation, and guided growth should be considered as a supplement to these soft tissue procedures.

Today, the postoperative evaluation is assessed using conventional pelvic radiographs. This will be performed at all 4 centres. To our knowledge, this study will be the first to evaluate changes after growth guided hip surgery in children with CP in a prospective randomized study.

Purpose:

The purpose of this study is to assess the skeletal growth and development of the bones after corrective Hip Surgery in children with CP using a transphyseal screw

Study Hypothesis:

The guided growth hip surgery is a safe and effective procedure to hip joint subluxation in the growing CP child.

Study design

This is a randomized prospective study, where patients are randomized to traditional surgery of tenotomies or tenotomies combined with guided growth of the hip. Thus, the following surgery will be performed in random order:

• Tenotomy of the hip adductors (longus) and Psoas (over the brim).
• Tenotomy of the hip adductors (longus) and Psoas (over the brim) complemented by guided growth of the hip by using a transphyseal screw.

The randomization is planned as an envelope extraction of codes. Randomization codes, lists and envelopes are prepared by an independent and uninvolved researcher. These are stored in a locked desk drawer at the sponsor's locked office at Hvidovre Hospital. If the investigator is not present, an independent secretary not involved in the project will have access to the randomization envelopes.

Patients will be included as participants by the following criteria:

Inclusion Criteria

- Between the age of 4 to 10 years
- Diagnosed with ataxic, hypotonic or spastic cerebral palsy
- GMFCS I - V
- Subluxation of 25-50 %

Exclusion Criteria

- No potential growth left in the proximal hip
- Subluxation less than 25 %

Patients that meet the below-described criteria will be asked to volunteer and informed consent from both parents will be obtained. The trial will be conducted longitudinally with evaluation at and after surgery. Follow-up with conventional pelvic radiographs will be performed at consecutive follow-ups after 12 and 24 months. This will be executed postoperatively (when admitted and within 3 days after surgery), after 12 and 24 months (+/- 3 weeks of visit window).
Moreover, pain evaluation will be performed in the post-operatively, after 4 weeks, 6 months, 12 months and 24 months. Evaluation of health-related quality of life will be performed using the CPCHILD questionnaire for GFMCS 3-5 and CPQoL for GFMCS 1-2 for the time points preoperatively and at 12 and 24 months.

Data registration

General information about the patient, general medical history pertaining to their CP and results from the surgery and radiographical images will be collected from the journal of each patient. All the information is part of the data needed to perform this study and is described in detail *under 'Exploratory endpoints*'. This information will also be passed on to government agencies during an inspection of the study if requested. However, all information regarding the patients will be protected according to "Lov om behandling af personoplysninger og Sundhedsloven, afsnit 3 ver. patienters retsstilling".

Radiological images will be stores at the treating hospital. Analysis and evaluation of the skeletal changes will be done ongoing their local software for radiological evaluation.

The data in this study will be registered and reported to the Danish data protection agency and will be stored in 10 years after the study has ended. Information regarding the patients will be protected according to "Lov om behandling af personoplysninger og Sundhedsloven, afsnit 3 ver. patienters retsstilling".

The results of this study (positive, inconclusive and negative) will be published in an international peer-reviewed journal, if external support for the expenses is granted. Upon publication of the study, data from the participants will be showed anonymously.

Inclusion process

We plan to include 52 children. All participants are recruited through the outpatient clinics at the local hospital and are typically referred from physicians specialized in the treatment of children with cerebral palsy or from the national register for CP, CPOP.

As the participants in this study all are minors, informed consent from both parents will be obtained thorough oral and written information about the study by the treating physician of the child, and the parents have had time to consider their child's participation in the study. Before the signing of the consent, the physician who already knows the child from the annual consultations will make sure that the participation in the study also follows the interest of the child.

The information about the study and the informed consent will be obtained in this order:

- The treating physician of the child will give oral information about the study to the child and their parents when they visit the hospital for their annual consultation. The information will be given in a closed and protected consultation room at the hospital.
- The parents and their child will also receive written information about the study and the brochures "før du beslutter dig" and "Forsøgspersoner rettigheder i sundhedsvidenskabeligt forskningsprojekt" , which they will take with them home. If

needed, they will be offered another information meeting, where they can bring an assessor.

- If the parents are not available at the annual consultation or they want to bring an assessor, another meeting will be set up, where the oral information about the study will be given
- The parents will be asked to read the information thoroughly at home before deciding and to contact the doctor as soon as possible if they want their child to participate or have additional questions. The parents will be contacted after a week if we have not received a response but are offered more time to consider their participation in the study if needed.
- Upon participation, the consent form will be signed by both parents at another consultation, a few days before the surgery.

Primary endpoints

Our primary endpoint is a measure of the guided growth of the proximal hip using conventional x rays measuring the migration index of the treated hip. This will be measured as a part of the clinical routine and is typically readily available in the national register of CPOP. This will be measured after 1 year.

A Reimers index. The length of the acetabular part of the femoral head remaining outside the lines and the total diameter of the femoral head as a ratio of these two measurements (the ratio of the outer acetabular part of the femoral head to the total diameter of the femoral head. The ratio was then multiplied by 100)

Secondary endpoints

Our secondary (primary) endpoints are secondary surgeries:

From 2 to 5 years post-operatively, revision surgeries defined as femoral osteotomies, pelvis Osteotomies, repeated soft tissue release, and repeated guided growth will be recorded.

Our secondary endpoints are also other relevant radiographical parameters:

A, Neck-shaft angle (NSA). The angle between a line down the axis of the femoral neck to the centre of the femoral head, and the axis of the femoral shaft.
B, Head-shaft angle (HSA). The angle between a line perpendicular to the widest portion of the head, and the axis of the femoral shaft.
C, Hilgenreiner-epiphyseal angle (HEA). The angle between Hilgenreiner line and a line drawn through the epiphyseal defect.
D, Femoral neck length (FNL). Length measured along the femoral neck axis, from the centre of the femoral head to its intersection with the axis of the femoral shaft.
E, Hilgenreiner epiphyseal angle. The angle is formed by a line drawn through the triradiate and a line drawn through the physes of the femoral head.

Exploratory endpoints

Explorative ends-points are pain level after surgery and quality of life. The CPCHILD questionnaire for GFMCS 3-5 and CPQol for GFMCS 1-2 will be used to evaluate the impact of the growth-guided procedure on the health-related quality of life. The questionnaire will be filled out before the surgery and after 12 and 24 months postoperatively

Pain evaluation will be performed post-operatively, after 4 weeks, 6 months, 12 months and 24 months using the pediatric pain profile.

Data ownership

Data will be held and owned by each centre. There will at data analyses to be anonymized for the analyses in the study.

Additional data

We will furthermore inquire about demography (age, gender, GMFCS), recovery time, time to full weight-bearing, and the occurrence of surgery-related complications that will be explored for later comparability with corrective surgery using osteotomies.

Status after pelvis osteotomies- clinical comparison.

For comparison, we will evaluate 22 children with CP operated on with pelvic osteotomies as a comparison to evaluate the level of pain and Qol as well as the radiographical parameters and the above additional data to compare them on a group level.

Sample size

The sample size estimation is based on the primary endpoint of the migration index measured by conventional pelvic radiographs. It is planned that 52 children with CP will be included. The study is planned as a superiority study. Based on the literature, it has been decided that a change in the primary outcome parameter of the hip migration index is considered relevant if the measured change constitutes a difference of at least 10 % measured by conventional pelvic radiographs [28]. We consider an absolute difference of more than 10 % to be superior; with a power of 95 %, and a β of 0.05 and an α of 0.05), a two-sided test would indicate that the sample size should be 46 patients (23 in each group). With an estimated dropout rate of six patients, a total of 52 patients will be included in the study. If more than four patients are excluded from the trial, additional patients will be included. Patients who have dropped out of the trial will be monitored, treated with standard treatment and followed up at yearly intervals.

Chronological Worksheet

1. Handing out or sending the written project information to parents.
2. Verbal information of the project by the surgeon before the surgery, and signing of the consent form by both caregivers and the surgeon.
3. Handing out the health-related quality of life questionnaire to the caregivers for the preoperative filling out.
4. Performing corrective surgery.
5. Day after the surgery: Conventional pelvic radiographs to confirm correct placement of plates/screw.

6. Conventional pelvic radiographs will be performed every year during the project. Pain scores and Qol questionnaires will be handed out when the patients are evaluated in the outpatient clinic.
7. Pelvic radiographs will be performed 12 months after surgery. At these recordings, the CPCHILD questionnaire will be handed out.
8. Another pelvic radiograph will be performed after 24 months before the screw used in the operation is removed. The health-related quality of life questionnaire will also be handed out and filled.
9. The guided growth screw is to be removed after 2 years by the operating centre.

Clinical examination and conventional x-rays as part of the routine follow up after corrective surgery.

Procedures

Surgical Procedure -Corrective hip surgery using guided growth

The patient is in a supine position. Preoperatively is given intravenously cefuroxime 100 mg/kg body weight, and half-dose is repeated after 2 hours. The surgeon will make a small (around 1 inch) incision on the lateral side of the proximal femur, through which a cannulated screw in the medial part of the physis of the femoral head will be inserted. The procedure only takes approximately a half-hour and the recovery time is short. The majority of children should be able to return to many of their normal activities within 1 to 2 weeks. Compared to traditional osteotomies, guided growth in principle is thus a safe procedure and a less invasive surgical method as proven by Stevens (24). The screw used in this procedure will be removed again after 24 months.

Postoperative mobilisation

Casting is not required after guided growth surgery, but due to the soft tissue surgery abduction casting is often required in 2-4 weeks. Full mobilisation is allowed afterwards in cooperation with the physiotherapy unit. As with any surgical procedure, pain is to be expected but should

be decreased during the first 1 to 2 weeks after surgery. Depending on comfort level and physician recommendations, the majority of children who undergo guided growth surgery should be able to return to many of their normal activities within 2 to 3 weeks.

XRAYS

In this study, we will include several radiographic measurements. This entails:

A, Neck-shaft angle (NSA). The angle between a line down the axis of the femoral neck to the centre of the femoral head, and the axis of the femoral shaft.
B, Head-shaft angle (HSA). The angle between a line perpendicular to the widest portion of the head, and the axis of the femoral shaft.
C, Hilgenreiner-epiphyseal angle (HEA). The angle between Hilgenreiner line and a line drawn through the epiphyseal defect.
D, Femoral neck length (FNL). Length measured along the femoral neck axis, from the centre of the femoral head to its intersection with the axis of the femoral shaft.
E, Hilgenreiner epiphyseal angle. The angle is formed by a line drawn through the triradiate and a line drawn through the physes of the femoral head.
F, Reimers index. The length of the acetabular part of the femoral head remaining outside the lines and the total diameter of the femoral head as a ratio of these two measurements (the ratio of the outer acetabular part of the femoral head to the total diameter of the femoral head. The ratio was then multiplied by 100)

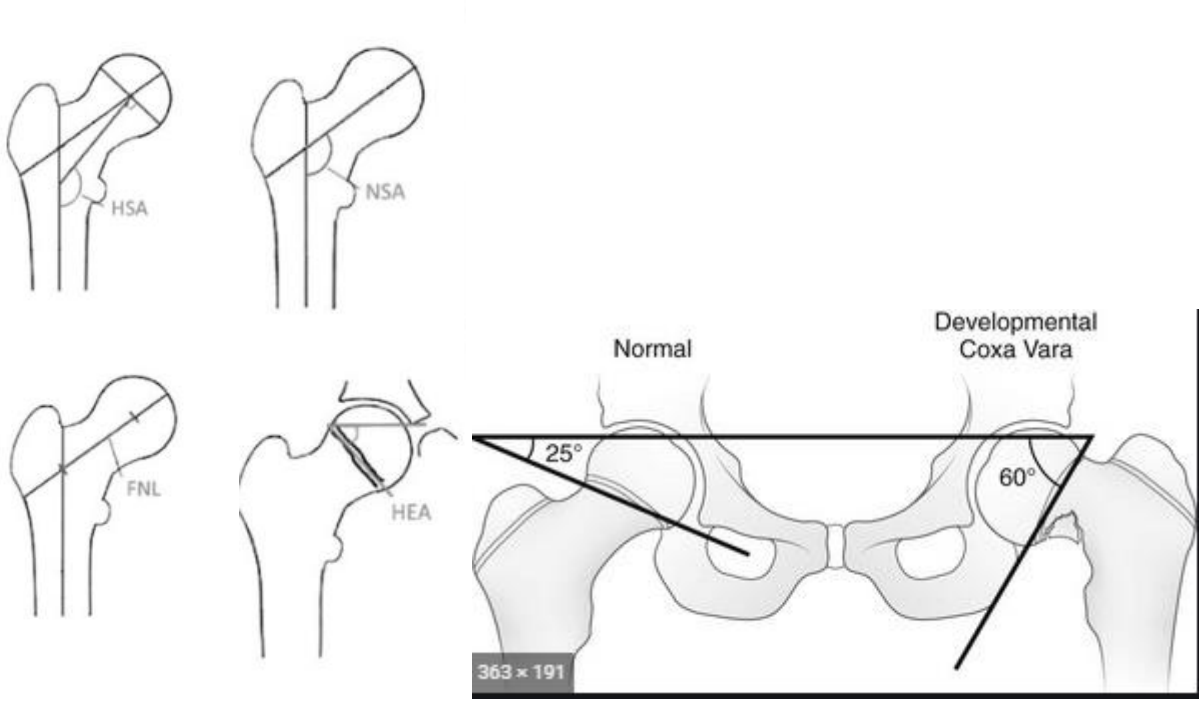

Figure 1. Selected radiographic parameters in the study.

Ethical Considerations

Corrective guided growth hip surgery

The children included in this study all need corrective guided growth surgery for their hip displacement (inclusion criteria: subluxation 30-40 %) as part of their treatment plan. Even though the guided-growth procedure is a fairly new procedure for the treatment of hip displacement, it is less invasive compared to osteotomies and earlier studies have shown promising results. Complications due to the surgery include infections and failure of growth arrest, and asymmetric physeal arrest leading to angular growth. However, these are all reversible problems that can be addressed accordingly. Tension band plates have been used to inhibit growth in anisomelic patients, but significant rebound growth is seen after this procedure making the risk of permanent growth inhibition small (25). However, the participation in this study does not increase the risk of complications, as the surgery is already part of their treatment plan.

This type of surgery can only be done if the bones in the hip are still able to grow and thus this

study can only be done in children. However, this study has the potential to document the benefits of choosing “guided growth” surgery to correct hip displacement instead of the more invasive osteotomy procedure, thus in our opinion the potential benefit of this minimally invasive and minimal intrusive procedure the child itself in this project as well as for future children outweigh the general surgical and anesthesiological risks since these children with certainty would be planned for the large surgical procedures instead of the above-described procedure or within a couple of years; this procedure might prevent this, based on the results from the current literature as described under ‘*introduction*’. Our experiences from an ongoing study with this procedure in the hip are, that it is safe and without complications and with early mobilization. However, we have seen in our study that such a screw has not been able to 'hold ' the growth zone/did not have adequate ingrowth and therefore the screw has had to be replaced. We, therefore, have a special screw for this surgery, where we have not yet seen this problem in connection with this surgery.

XRAYS

Conventional pelvic radiographs will be performed as part of the patient's clinical follow-up, thus will not induce any additional radiation due to the study.

Funding

This study is independent and initiated by a group of medical doctors at all 4 pediatric orthopaedic surgical centres of Denmark. The study is self-financing by these hospitals and thus commercial funding does not support the study. However, the funding only covers the expenses connected to the execution of the study. Expenses connected to the publication of this study have to be funded externally. Both the Danish Research Ethical Committee and participants will be informed about the external funding if granted.

Publication:

The results of this study (positive, inconclusive and negative) will be published in an international peer-reviewed journal and at national or international conferences. Upon publication of the study, data from the participants will be shown anonymously. All co-investigators will be offered authorship of such publication and the conditions, that each

participating partner/centre have included, treated one forth of participants with 2 years evaluation as described above. The publication will not be affected by the other interests of organizations or otherwise. Up till two authors will be included from each centre after an external agreement.

Upon signing of consent, all participants will be offered to receive written information about the main results of the study and their scores in the study after the study has ended.

Timetable:

1. The inclusion period is expected to be 36 months with consecutive inclusion of 22 patients

2. The follow-up measurements and data analysis will be performed meanwhile and after inclusion (2-2½ year).

3. In the following year after the study has ended, articles for an international peer-reviewed journal will be written, if external funding for the expenses is received.

This study is planned to end on 30 December 2025.

Collaborators:
The Orthopaedic Department, Hvidovre Hospital.
The Orthopaedic Department, Aalborg Hospital.
The Orthopaedic Department, Rigshospitalet.
The Orthopaedic Department, Odense Hospital.

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tillægsprotokol 71226 til projekt H-17021841 date16-08-2021