June 6, 2019

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Study Title: Effect of Steroids on Post-Operative Complications Following Proximal Hypospadias Repair

Study Objective:
The primary objective of this study is to determine the efficacy of administering a short course of postoperative oral steroids in pediatric patients undergoing proximal hypospadias repair as prevention against complications. Specifically, the study aims to assess if the use of steroids i) decreases the incidence of fistula formation, glans dehiscence, wound breakdown, meatal stenosis, urethral stricture formation, or diverticula formation, and the need for subsequent redo-hypospadias surgeries and/or fistula repairs and ii) improves the quality of wound healing including the overall cosmetic appearance of the phallus (i.e. the location of the urethral meatus).

Study Design:

This is an experimental study that will be prospective, randomized, placebo-controlled, and double-blind. There will be no cross-over arm.

Primary and secondary study endpoints:

The study aims to assess if the steroids i) decrease the incidence of glans dehiscence, wound breakdown, fistula formation, meatal stenosis, urethral stricture formation, urethral diverticulum formation, meatal regression, and the need for subsequent redo-hypospadias surgeries and/or fistula repairs and ii) improve the quality of wound healing including the overall cosmetic appearance of the phallus (i.e. location of the urethral meatus)
The catheter removal visit (7-10 days after surgery) & the initial follow up visit (6-12 weeks after surgery) as well as data from 1 year postoperatively, after toilet training, and after puberty. We plan to analyze and present preliminary data when we have data on a significant cohort from the first 2-3 timepoints as it will be many years until we have the post-puberty followups since we operate on these subjects, on average, under age 2 or so.

Inclusion criteria:
All male patients' ages ranging from 3 months to 16 years seen at Department of Urology and diagnosed with hypospadias will be included in this study.

Exclusion criteria:
Patients taking steroids at the time of surgery or within six weeks of surgery
Patients with a history of steroid hypersensitivity reactions
Patients who are immunocompromised or taking immunomodulatory medications
Patients with fungal infections
Females

Selection will be based on parent willingness to allow the child to participate in the study.

Enrollment goal: 300

Recruitment methods:

The clinician will discuss the project during the routine clinical exam and provide an age appropriate explanation with the patient and the patient's parents. If the patient's parents and patient express interest in study participation, the clinician will provide the parents and patient with the IRB approved informed consent document during the subject's routine clinical exam. During the initial visit in the Urology Outpatient Clinic, the clinical diagnosis of hypospadias will be made by a physician, nurse practitioner, or a physician assistant. An initial documentation of the degree of hypospadias will be made. The patients will be scheduled to undergo surgery to repair the hypospadias when it is clinically indicated, and surgery will typically take place when the child is between 6 and 12 months of age. The age range for this study will be 3 months to 16 years to allow for collection of data during follow up visits until the subjects reach puberty. Ideally, the surgeon or a co-investigator will review the study with the parent of the patient during the child's diagnostic-surgical listing visit and, if participation is desired, the surgeon will obtain written informed consent. If the consent is not obtained at the diagnostic-surgical listing visit, a co-investigator will contact the parent by telephone 1-2 weeks prior to listed surgery to explain the study and inquire if there is interest in participation; if so, the consent form will be mailed or faxed to the parent for review. The purpose of this pre-surgery phone call is to eliminate any coercion that might play a role if the study were to be introduced to the parent on the day of the surgery alone and to give the parent time to consider the study before agreeing to participate. These patients will be identified at the existing weekly Division of Pediatric Urology Pre-Operative conference at which the surgeons/co-investigators meet to review the upcoming listed cases. A co-investigator will then meet with the interested parent on the day of the surgery to answer any questions as well as to review the study and consent form. If the parent wishes to enroll their child in the study at this point, the surgeon will obtain written and verbal consent for participation. The decision about whether or not to participate in the study will not change the type or the quality of the surgery that is performed.

Purpose, specific aims or objectives, and hypotheses to be tested:

The primary objective of this study is to determine the efficacy of administering a course of postoperative oral steroids as a preventative measure against complications/a means of enhancing repair in patients undergoing surgery for proximal hypospadias.

It is our hypothesis that a short course of postoperative steroids will facilitate healing of hypospadias to the degree that it will minimize the risk of wound complications. This hypothesis is based on the known scientific effects of corticosteroids on healing as well as the experience of the senior investigator. It is only through completion of a prospective, double-blinded, randomized, placebo-controlled study that we will be able to clearly and convincingly demonstrate that the risks of wound complications is significantly lowered with steroids to justify their routine use in this patient population.

Relevant prior experience and gaps in current knowledge. Scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:

Proximal hypospadias repair is a surgery for males who are born with an abnormally located urethral meatus that can be on the proximal third of the shaft of the penis, at the penoscrotal junction, in the scrotum, or on the perineum. With this procedure, a urethra is constructed and pathologic penile curvature is corrected in order to relocate the meatal opening to the glans penis. The goals of hypospadias surgery are to allow for normal function of the penis, which includes the ability to void a straight, non-obstructed urinary stream without spray or dribbling, to have a straight erection, and to propel ejaculate, with a normal penile appearance. Unfortunately, proximal hypospadias repair has a relatively high postoperative complication rate (reports range from 12-60% with a sum 207/677 [31%] from: Aoki, 2008; Bush, 2013; Braga, 2007; Chuang, 1995; Ghanem, 2011; Gopal, 2008; Hayashi, 2007; de Mattos e Silva, 2009; Powell, 2000; Shukla, 2004; Snodgrass, 2011). The known complications include fistula formation, glans dehiscence, wound breakdown, meatal stenosis, urethral stricture formation, diverticula formation, and meatal retraction with a poor cosmetic result, and all of these require surgical treatment under general anesthesia.

As a result, past efforts have been made to determine risk factors for known complications, which has led to the identification of the meatal location as the most significant risk factor for development of a postoperative complication in primary hypospadias repair.(Bush, 2013) Regrettably, this factor is inherent to the degree of the disease that the child presents with at the time of diagnosis and thus, is not modifiable. Potentially modifiable factors such as type of suture material, suturing technique, surgeon, and use of a urethral stent have not been found to be associated with post-operative complications. Because the high risk for postoperative complications has persisted over the past decades, efforts are needed to identify novel ways in which the high complication rate and associated morbidity can be reduced.

Surgeons have been greatly interested in the effects of corticosteroids on wound healing for years as steroids have been shown to affect all major steps of the wound healing process, which is divided into 3 overlapping phases known as inflammatory, proliferative, and remodeling. In fact, it is due to a presumed attenuation of the inflammatory phase that steroids have been shown to improve the rate of healing.(Bosanquet, 2013) Nonetheless, there have been no published studies on how steroids would influence healing as related to hypospadias repair and, in turn, the associated complication rate. It is reasonable to assume that there may be some benefit from the use of corticosteroids as they are known to decrease the expression of cytokines in wounded tissue including TGF-b1, platelet-derived growth factor, tumor necrosis factor, and interleukin-1a. This action decreases the chemotactic and mitogenic stimulus for other inflammatory cells and the infiltration of polymorphonuclear leukocytes. Additionally, corticosteroids reduce mesenchymal cell expression of keratinocyte growth factor, which alters fibroblast proliferation such that application of a steroid to a wound will delay re-epithelialization,(Wang, 2013; Namkoong, 2013) and the resultant decreased type I procollagen synthesis will cause wounds to heal with reduced contraction,(Franz, 2007; Bosanquet, 2013) a desired outcome in hypospadias repair in particular given the need for tubular healing free of narrowings that can generate turbulence or wall pressure changes. While wound tensile strength has been shown to decrease in animal studies when cortisone is chronically administered at a dose of 15-40 mg/kg/day,(Wang, 2013) systemic high-dose steroids (30 mg/kg methylprednisolone, which is 5-13 times greater strength than the doses used in the animal studies) have been shown in a randomized, double-blind, placebo-controlled trial in humans not to negatively impact wound infection or dehiscence rates, more clinically relevant measures, instead benefitting patients in the postoperative period in ways such as decreasing pain.(Schulze, 1997) Additionally, a Cochrane review of 54 randomized studies of adult cardiac surgery patients found that prophylactic corticosteroids did not increase postoperative infection or impair wound healing.(Dieleman, 2011) Of note is that the beneficial findings were associated with acute as opposed to chronic steroid use.

While the long-term use of oral corticosteroids is associated with a variety of negative side effects, the pediatric asthma population is one that has demonstrated how adverse effects of oral corticosteroids “are rarely if ever associated with short courses of steroids.”(Weinberger, 1982) Because an acute course of oral systemic steroids has been so routinely used in patients under the age of 12 with asthma exacerbations (liquid prednisolone at 1-2 mg/kg/day in 1-2 divided doses for up to 10 days, although usually given for 5 days, which is at least 19 times less than the dose proven to be safe in the randomized controlled trial mentioned above) and proven to be safe, we believe that the above sum findings and the clinical observations of our senior investigator support a randomized placebo-controlled trial to evaluate whether a 5-day post-operative course of oral prednisolone at a dose of 1.5 mg/kg/day divided into two doses leads to improved outcomes in patients who have undergone surgical repair of hypospadias.

Detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study:

Screening procedures will consist of a medical history and physical examination pre- and post-operatively that are the same as the standard exams and medical/surgical workup that any patient would receive whether or not enrolled in the study.

During the initial visit in the Urology Outpatient Clinic, the clinical diagnosis of hypospadias will be made by a physician, nurse practitioner, or a physician assistant. An initial documentation of the degree of hypospadias will be made. The patients will be scheduled to undergo surgery to repair the hypospadias when it is clinically indicated, and surgery will typically take place when the child is between 6 and 12 months of age. The age range for this study will be 3 months to 16 years to allow for collection of data during follow up visits until the subjects reach puberty. Ideally, the surgeon or a co-investigator will review the study with the parent of the patient during the child's diagnostic-surgical listing visit and, if participation is desired, the surgeon will obtain written informed consent. If the consent is not obtained at the diagnostic-surgical listing visit, a co-investigator will contact the parent by telephone 1-2 weeks prior to listed surgery to explain the study and inquire if there is interest in participation; if so, the consent form will be mailed or faxed to the parent for review. The purpose of this pre-surgery phone call is to eliminate any coercion that might play a role if the study were to be introduced to the parent on the day of the surgery alone and to give the parent time to consider the study before agreeing to participate. These patients will be identified at the existing weekly Division of Pediatric Urology Pre-Operative conference at which the surgeons/co-investigators meet to review the upcoming listed cases. A co-investigator will then meet with the interested parent on the day of the surgery to answer any questions as well as to review the study and consent form. If the parent wishes to enroll their child in the study at this point, the surgeon will obtain written and verbal consent for participation. The decision about whether or not to participate in the study will not change the type or the quality of the surgery that is performed.

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The type of hypospadias repair will be determined by the surgeon in the operating room at the time of the surgery based on the clinical scenario. Children will be excluded if they are found upon the exam under anesthesia in the operating room at the time of surgery not to have proximal hypospadias. The final severity of the hypospadias will be documented by the surgeon based on an examination performed in the operating room under anesthesia just prior to initiation of the surgical repair. The need for short-term postoperative stenting will be decided at the time of the procedure. After the procedure, the pharmacy will deliver the medication, prednisolone versus placebo which will be blinded from the parents as well as the surgeon, to the OR and the surgeon will bring the medication to the families after surgery. At that time the parents are instructed on how to administer the steroid or placebo, twice daily for 5 days. This constitutes the focus of the study and is the only variation from standard treatment. Parents will be instructed to call for any suspected adverse reaction to the medication versus placebo and for any findings consistent with glans dehiscence, wound breakdown, fistula formation, diverticulum formation, meatal stenosis, or urethral stricture.

All patients will be seen by the surgeon in postoperative follow up in the Urology Outpatient Clinic 7-12 days after the surgery following completion of the 5-day course of prednisolone versus placebo. Stents will be removed at this time as is standard practice. The next follow up will be at 4 to 12 weeks postoperatively as is standard practice. At a minimum, participants will be asked to follow up again at 6-months postoperative, and after toilet training, and possibly one year after puberty up until 16 years of age, which does not deviate from standard practices. Each postoperative visit will include evaluation for glans dehiscence, wound breakdown, fistula formation, diverticulum formation, the presence of meatal stenosis, the presence of a urethral stricture, and the location of the urethral meatus/cosmetic appearance of the phallus in addition to the quality and progression of wound healing and the quality of the urinary stream. Any phone calls, emergency room, or office visits that take place outside of the scheduled follow-up visits will be tracked so that a phone or office interview can be arranged to make similar assessments if they are not made at the time of those encounters. Any return to the operating room for redo-hypospadias surgery as well as the intraoperative physical exam and findings will be noted. Any adverse events associated with the medication or placebo will be noted and classified in terms of severity, expectedness, and association with the medication or placebo.

Data will be stored in RedCap, a secure server with de-identified patient information that can be accessed only by investigators on the study using their individualized usernames and passwords. Data analysis will be made on at least an annual basis to allow for early termination of the study in the case that one arm is unequivocally superior or inferior.

Power analysis used and method of statistical analysis:

We will need to enroll 64 patients in the study to reject a false null hypothesis if we assume that the complication rate for proximal hypospadias surgery is 30% and that the administration of prednisolone for five-days postoperatively at a dose of 1.5 mg/kg/day divided into two doses will decrease that rate to 5%. We will need to enroll 196 patients in the study to reject a false null hypothesis if we assume that the complication rate for proximal hypospadias surgery is 25% and that the administration of prednisolone for five-days postoperatively at a dose of 1.5 mg/kg/day divided into two doses will decrease that rate to 10%. For this reason, we would like to accrue roughly 200 patients in the study, however, we will run statistical analyses at least yearly so that the study can be concluded early if indicated.

Patients will be randomized by the research pharmacist with help from the statisticians at the Clinical and Translational Science Institute (CTSI) here at the University of Pittsburgh. The research pharmacist at Children's Hospital of Pittsburgh will blind the researchers/surgeons to the identity of the oral solution (steroid versus placebo) being administered. The placebo group will serve as the study control to determine the change in complication rate achieved through the use of steroids.

Statistical Analysis Plan:

Demographic measures (median gestation, weight, follow-up in months, incidence of NICU stay, and incidence of comorbidities) will be compared between the steroid and placebo arms using appropriate statistical approach, i.e., t-tests, Fisher's Exact test, or Wilcoxon Rank-sum test.

We were unable to meet our enrollment goal sufficient to test our hypothesis for each complication (meatal retraction, meatal stenosis, glans dehiscence, skin breakdown along suture lines, urethra breakdown proximal to glans, urethrocutaneous fistula, suspected stricture, and suspected urethral diverticulum), therefore the incidence of complication overall between the steroid and placebo groups will be analyzed using Fisher's Exact Test.

Likewise, Fisher's Exact Test will be used to test the quality of wound healing, including the location of the urethral meatus (subcoronal, distal shaft, proximal shaft, penoscrotal, scrotal perineal, and other), and the improvement of chordee (resolved/ improved/ described but not documented/ no improvement/ not described) in each category (degloving, ventral, and plication).