Official Study Title – Gentamicin Intravesical Efficacy for Infection of Urinary Tract

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The following document contains a portion of the research plan for this study approved by the UC San Diego on June 6, 2020. This portion of the research plan outlines the study protocol and statistical analysis plan.

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microscopic level not previously well studied.

8. PROGRESS REPORT

Not applicable

9. RESEARCH DESIGN AND METHODS

Overview

This is a prospective, randomized**,** single-blinded (subject), two-parallel armed, comparison of a single postoperative intravesical instillation of 80 mg of gentamicin sulfate in 50 mL of saline with no instillation on the proportion of women treated clinically for UTI within 6 weeks after undergoing urogynecologic surgery.

The randomization scheme will be stratified based on the type of urogynecologic surgery performed given that different risk factors for post-operative UTI depending on type of surgery. Transvaginal, versus transabdominal, prolapse surgeries have a higher rate of post-operative UTIs. Midurethral sling surgery also increases the risk for UTI compared to a surgery without. Additionally, our planned second site Kaiser Permanente performs relatively more transabdominal prolapse repairs than is done at UCSD. Therefore we plan the following strata with a 1:1:1:1 allocation between the strata: (1) transabdominal prolapse repair with midurethral sling, (2) transabdominal prolapse repair without midurethral sling, (3) transvaginal prolapse repair with midurethral sling, and (4) transvaginal prolapse repair without midurethral sling.

Study Procedures/Activities

A woman scheduled to undergo urogynecologic surgery will be informed by her surgeon she is eligible for study enrollment at her standard-of-care pre-operative appointment. At that time, if the patient wishes, written informed consent will be obtained and the patient will be assigned a study identification (ID) number. On the day of surgery, the patient will meet with her surgeon briefly again in the pre-operative area to confirmed continued design to participate in the study and to review the surgical plan. Premenopausal subjects (i.e. last menstrual period less than 1 year ago) who have not previously undergone hysterectomy undergo a urine pregnancy test as part of their standard clinical care to assure non-pregnant status on day of surgery. The results of this test will be utilized to determine final study eligibility, i.e. those who are determined to be pregnant will be excluded from the study. Regardless of study group assignment, the subject will receive pre-operative intravenous prophylactic antibiotics, which is the standard of care per hospital policy. Once the subject is in the operating room and has undergone induction of anesthesia and placement of a transurethral catheter for clinical care, a urine sample will then be obtained at the start of the case. A vaginal swab will also be obtained. The process of obtaining these samples will take less than 1 minute and will not significantly prolong anesthesia time. These samples will be saved for microbiome analysis. The planned surgery will then be performed. Then, while still under general anesthesia and during the final safety cystoscopy performed for the subject's standard clinical care, if the patient has not had any intraoperative events that exclude her from the study, the surgeon will open the patient's randomization envelop to determine study arm assignment (to gentamicin or no instillation group). After a final foley catheter is placed, for the subject's standard clinical care, another urine sample for microbiome analysis will be obtained, as will a vaginal swab for vaginal microbiome analysis. Then, if the patient is randomized to gentamicin, 80mg of gentamicin in 50 mL of normal saline will be infused into the patient's bladder through the standard-of-care transurethral catheter by the surgeon. The surgeon will then clamp the catheter and label the catheter with the clamping time. If the patient is randomized to no instillation, the surgeon will clamp the catheter and label the catheter with the clamping time. The purpose of clamping the catheter for subjects receiving usual care will be to ensure patients are blinded if they wake up and notice their catheter. The subject will then proceed

as usual to the postoperative anesthesia care unit (PACU), with instructions for the PACU nurse to unclamp the catheter 1 hour after the clamping time. All patients will then receive usual postoperative care including an active voiding trial as indicated. During the voiding trial, which is performed as part of the subject's standard clinical care, the transurethral catheter is disconnected from the collection bag. Then the subject's bladder is backfilled with approximately 300 mL of sterile water or saline. The catheter is then removed and the patient is instructed to urinate. The voided volume is measured. The post-void residual is also measured non-invasively by bladder scan.

After surgery, as is part of routine care, the patients will call the surgeon's office if they have UTI symptoms and these calls will be addressed in the usual fashion by the nursing and physician office staff. The patients will give catheterized urine samples as indicated for UTI symptoms which will be processed at a UCSD laboratory.

At 6 weeks after surgery the patient will be seen for a standard-of-care postoperative appointment. At this time, the patient will undergo some standard-of-care health questions related to post-operative healing and any adverse health events since surgery. For the specific purposes of the study and at the FDA's recommendation, all patients at the 6 week post-operative visit will be asked whether they have experienced new onset of hearing loss, tinnitus, dizziness, or vertigo since surgery. For the purposes of the study, if the patient does not come to their post-operative appointment, they will be called at to see whether they have been treated for UTI or have UTI symptoms since surgery. They will also be asked about any other adverse health events since surgery.

Schedule of Participant Visits

Visit	Timing	Purpose	Location	Time Required	Testing
1	Within 4 weeks of surgery	Standard-of-care preoperative counseling, study recruitment and informed consent process	WPMC	60 minutes	Standard-of-care complete blood count, serum electrolytes, serum creatinine and blood urine nitrogen, pregnancy test for women of childbearing potential, and urinalysis and/or urine culture for all patients
2	Day of Surgery	Surgery, Randomization, Study Intervention (gentamicin instillation versus only catheter clamping), Standard-of-care post-operative care	JMC/KOP	Approximately 8 hours (depending on surgery length)	Standard of care pre-operative pregnancy test for appropriate patients, 2 catheterized urine specimens and 2 vaginal swab specimens for microbiome analysis
3	6 weeks after surgery day	Standard-of-care postoperative assessment	WPMC	60 minutes	Standard of care urinalysis and/or urine culture if UTI symptoms

Procedures/Interventions Performed Solely For Research Purposes

The procedures/interventioned performed solely for research purposes include the collection of urine samples and vaginal swab samples immediately before and after the urogynecologic surgery, as well as the instillation of gentamicin (if randomized to that arm), and the clamping of the catheter in both study arms. Post-operative questions regarding new onset of hearing loss, tinnitus, dizziness, or vertigo since surgery are also specifically for the study due to the FDA's recommendation in the IND

approval process. Finally, the telephone call at 6 weeks if the subject does not come to their scheduled follow up appointment will be for the purpose of collecting study data. All other aspects of the study are routine clinical care that the subjects would be undergoing even if they were not participants in the study.

IND Requirement

Gentamicin sulfate is FDA approved for treatment and prevention of bacterial infections in adults given by intramuscular or intravenous route. Our study proposes the use of gentamicin sulfate 80mg in 50 mL of normal saline administered directly into the bladder via transurethral catheter to prevent post-operative UTI infection. The subject would have this standard-of-care catheter at the end of the surgery regardless of participation in the study. Due to our proposal for a new route and indication, and Investigational New Drug application has been filed with the FDA (IND 146413) and we have been cleared to proceed with this proposed trial as of November 15, 2019. See attached documents for IND correspondence with the FDA.

Study Procedures for Obtaining Research Material

All research material will be stored labeled with subject study ID rather than identifying characteristics. All material will be collected specifically for research purposes and will not be saved for future use after the current study is concluded. Urine samples will be collected by a transurethral catheter placed as part of the subject's standard clinical care immediately before and after the surgery while the subject is still under general anesthesia. Vaginal swabs will be collected at the same time. Other study material will be collected by manual abstraction of data from the electronic medical record. No audio or video recording will be performed as a part of the study. No questionnaires will be used for the study.

Data Collection

An encrypted electronic database will be used to compile study data. All subjects will have a unique study ID linked to protected health information stored separately in a locked room at WPMC only accessible to study personnel. The data will be entered into the database by study ID.

Baseline subject data will be collected including patient name, medical record number, date of birth, telephone call for phone follow up, age, body mass index (BMI), parity, race, ethnicity, prior hysterectomy, history of diabetes mellitus, American Society of Anesthesiologists (ASA) Physical Status Class, menopausal status, use of hormone replacement therapy within 3 months, use of vaginal estrogen within 3 months, history of recurrent UTI, and positive pre-operative UTI.

At the end of each surgery, the surgeon will record the following information on an OR Form which will be later entered into the data base – procedures performed, procedure start and end time, number of cystoscopies, resident and/or fellow involvement and year of training, estimated blood loss, IV antibiotic received pre-operatively and whether or not it was appropriately re-dosed as indicated. These OR forms will be kept in a secured box in the Women's Pelvic Medicine Center with only co-investigators and study staff having access. The OR forms will be labeled by study ID.

The following information will be extracted from the patient's chart for the post-operative period - length of hospital stay in days, length of initial immediate post-operative catheterization (in days), results of initial active voiding trial, need for continued postoperative catheterization after hospital discharge (and if so -, type of post-operative catheterization [indwelling or intermittent] and duration [in days]), post-operative UTI treatment and urine culture result if applicable, patient reports of dizziness, tinnitus, hearing loss, or vertigo, and hospital readmission. This information will be added to the electronic database.

Results of intraoperative urinary and vaginal microbiome results will also be added to the electronic database.

Prior to final analysis, the investigators will make efforts to resolve any missing data by a final review of the electronic medical record.

Based on previously published data regarding safety of intravesical gentamicin, we will focus specifically on gathering data related to suprapubic discomfort and development of antibiotic-resistant UTI.[14,15] Other adverse events during the study period, including death and hospital admission, will also be recorded. Per FDA request we will also monitor for ototoxicity including dizziness, vertigo, hearing loss, and tinnitus. Study investigators will review the study database every 6 months to analyze incidence of adverse events. If there is a 10% or greater incidence of serious adverse event among participants (i.e. unanticipated hospital admission), the research team will meet to discuss potential for serious adverse event to be related to intravesicular gentamicin, study modification, or termination.

Data Analysis/Interpretation

Subjects' data will be analyzed "as treated". Preoperative and perioperative variables will be summarized by means with standard deviations for continuous variables and rates and proportions for categorical variables. To determine whether any significant baseline differences exist between the study arms, preoperative and perioperative variables of the two study arms will be compared using chi-square test for categorical variables or Student t-test or Wilcoxon rank sum test for continuous variables.

The primary outcome of the study, proportion of patients who are clinically treated for UTI, will be analyzed with a chi-squared test. All adverse events will be listed with description of type and severity. The proportion of patients with each type of postoperative adverse event (diarrhea, yeast infection, hospital admission with organ dysfunction, and death) in each arm will also be compared using a chi-squared test. Statistical significance will be defined as $\alpha<0.05$.

In order to perform our sample size calculation, we first wanted to baseline postoperative UTI rates according to the definition of our primary outcome at our institution. Chart queries were performed for all GIVE-IT candidates during 2-month time period (Jan-Feb 2019; N=41) at Kaiser San Diego (our FPMRS fellowship sister institution), as it is currently our practice at UCSD (but *not* at Kaiser) to prescribe oral antibiotic prophylaxis following SUI surgery, which could alter UTI rate. The UTI rate in this chart query was 17%. To detect a meaningful reduction in UTI from 17% in controls to 8% in intervention group ($\alpha = 0.05$, one-tailed) with 80% power ($\beta = 0.2$), 166 subjects will be needed per arm. This effect of 50% reduction as a meaningful outcome is derived from the similar effect of oral antibiotic post-operative UTI prophylaxis seen in a similar clinical trial.[3] Accounting for 20% dropout or loss to follow-up, we will recruit 200 subjects per arm. Our benchmark for successful recruitment will be approximately 50% recruitment completed 6 months after the first subject is enrolled. In order to complete enrollment more rapidly, we anticipate adding Kaiser San Diego as a secondary study site.

All of the patients in the study will be women. Based on a retrospective population-based cohort study of 149,554 American women, there was an 11.1% lifetime risk of undergoing a single surgery for prolapse or incontinence by age 80.[17] In another population based cohort study of 2270 middle-aged and older racially diverse American women (44% white, 20% African American, 18% Asian, and 18% Latina or other), 19% of the Latina women, 7% of the Asian women, and 5% of the African American women reported bothersome prolapse.[18] A study of the same cohort found that 36% of Hispanic women, 25% of African American women, and 19% of Asian America women reported weekly urinary incontinence.[19] The study will not specifically recruit or exclude minority ethnic groups. Based on the clinical population at WPMC, approximately 30% of the subjects are expected to be Latina, 10% Asian, and 5% African American.

10. HUMAN SUBJECTS