Fellows' Pelvic Research Network (FPRN)
MANUAL OF PROCEDURES/PROTOCOL

A randomized, double-blind, placebo-controlled trial of nitrofurantoin prophylaxis in women undergoing short-term catheterization for acute postoperative urinary retention after pelvic reconstructive surgery

PI: Erin Seifert Lavelle, MD
Mentor: Gary Sutkin, MD

Data Coordinating Center
Magee Womens Hospital of UPMC
University of Pittsburgh
Pittsburgh, PA

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ABSTRACT

The specific aim of this randomized double-blind placebo-controlled trial is to determine if extended release nitrofurantoin antibiotic prophylaxis decreases the incidence of symptomatic urinary tract infection (UTI) compared with placebo for patients undergoing short term indwelling or clean intermittent self-catheterization (CISC) for acute postoperative urinary retention following pelvic organ prolapse and/or urinary incontinence surgery.

Consented patients who undergo urogenital surgery and fail their post-operative voiding trial will be randomized to either extended release nitrofurantoin 100mg or an identical appearing placebo capsule to be taken daily while performing CISC or while indwelling catheter is in place. The primary outcome will be symptomatic and culture confirmed UTI within six weeks of surgery. Secondary outcomes include adverse events associated with nitrofurantoin use, and incidence of nitrofurantoin-resistant isolates from urine culture of symptomatic women.

Primary and secondary outcomes will be evaluated with Student t test and chi squared or Fisher exact test as appropriate. Assuming a decrease in symptomatic UTIs attributable to nitrofurantoin prophylaxis from 33% to 13%, with 80% power, and a two-sided alpha of 0.05, and a 10% dropout rate, we should recruit a total of 154 patients.

SPECIFIC AIMS

Primary Aim: To determine if extended release nitrofurantoin administered daily to patients using indwelling or clean intermittent self-catheterization (CISC) after pelvic organ prolapse and/or urinary incontinence surgery will decrease the incidence of symptomatic and culture proven urinary tract infection (UTI) when compared to placebo in a randomized, double-blind trial.

Secondary Aim(s): To determine how nitrofurantoin antibiotic prophylaxis administered to patients using an indwelling catheter or CISC after pelvic organ prolapse and/or urinary incontinence surgery affects frequency of adverse events related to daily nitrofurantoin exposure, and frequency of urine cultures positive for nitrofurantoin-resistant isolates.

The Null Hypotheses: Nitrofurantoin antibiotic prophylaxis administered to patients using an indwelling catheter or CISC after pelvic organ prolapse and/or urinary incontinence surgery does not change the incidence of symptomatic and culture proven urinary tract infection (UTI) compared with placebo.

BACKGROUND

Urinary tract infections (UTI) occur frequently following surgery for urinary incontinence or pelvic organ prolapse (POP), with reported incidence up to 48% (Albo 2007, Chai 2009, Sutkin 2010, Nygaard 2011, Wei 2012). This high rate is frequently attributed to intraoperative factors, such as manipulation of the genitourinary tract and instrumentation of the bladder and urethra, as well as an approximately 50% rate of short

term postoperative catheterization following urogynecologic surgery (Sutkin 2010, Nygaard 2010, Dieter 2014). As American women have a 20% lifetime risk of surgery for POP or urinary incontinence, the absolute number of women at risk for urinary infectious morbidity associated with these procedures is quite high (Wu 2014).

The substantial risk of UTI following POP or incontinence surgery, combined with the well-established risk associated with catheterization, leads many practitioners to prescribe oral antibiotics to women undergoing catheterization in the postoperative period. However, there is minimal Level I evidence to support or refute this practice. The Infectious Disease Society of America (IDSA) Guideline acknowledges that prophylactic antibiotics have been shown to reduce UTI rates among patients using short term postoperative catheterization in randomized trials (Hooton 2009). However, they recommend against routine antibiotic prophylaxis use due to concerns regarding anti-microbial resistance, cost, and potential for adverse effects, even among high risk groups including women undergoing urogynecologic surgery. This recommendation is based on expert opinion, given a paucity of trial data to guide clinical care.

Nitrofurantoin is a commonly used antibiotic for UTI prophylaxis during catheterization, is well-tolerated with few adverse effects, and is known to have a very low rate of associated resistance (Shaw 1989). After decades of use, it remains active against the most common UTI pathogens that have gained resistance to other antimicrobials (Guay 2001). For example, in the 2013 Magee-Womens Hospital Adult Antibiogram, 98% of E-coli specimens were sensitive to Nitrofurantoin, which has been consistent since at least 2007. The drug has a half-life of 20 minutes and 40% is concentrated in and excreted into the urine in a therapeutically unchanged form. Thus it has minimal impact on vaginal and bowel flora. Nitrofurantoin has been shown to reduce the incidence of positive urine cultures and symptomatic UTIs in women with a suprapubic catheter after pelvic organ prolapse and/or urinary incontinence surgery (Rogers 2004). No trials have evaluated nitrofurantoin prophylaxis for women using short term indwelling catheters or CISC following urogynecologic procedures.

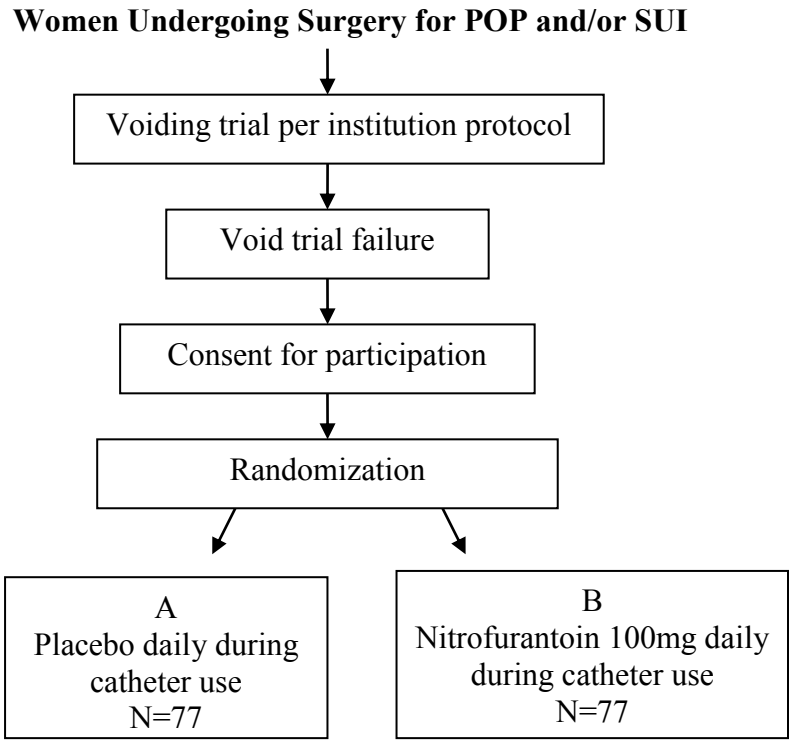
Given the large number of women at risk for urinary infectious morbidity associated with short term catheterization for acute urinary retention following POP and/or incontinence surgery, and the paucity of data on the impact of antibiotic prophylaxis in this setting, we propose to demonstrate the efficacy of nitrofurantoin prophylaxis through an adequately-powered, placebo-controlled trial. Secondary outcomes will include adverse events associated with nitrofurantoin use, and incidence of nitrofurantoin resistant bacterial isolates from urine culture.

SIGNIFICANCE

This prospective, randomized control study is uniquely feasible in the Fellows' Research Pelvic Network, where data from a large and diverse patient population can be collected.

STUDY DESIGN

Women who undergo surgery for urinary incontinence and/or pelvic organ prolapse who fail a post-operative voiding trial will be eligible to participate in this a double blind, randomized trial. Randomization will be a block randomization stratified by site with 1:1 allocation to either extended release nitrofurantoin 100mg or an identical appearing placebo capsule to be taken daily while using an indwelling catheter or performing CISC. Neither the patient, nor her physician nor the research staff will know her allocation. The diagram below outlines randomization details:



Inclusion criteria: Women who have undergone surgery for the correction of pelvic organ prolapse and/or urinary incontinence and failed a postoperative voiding trial and provide informed consent will be randomized.

Exclusion criteria: Known drug allergy to nitrofurantoin, a history of renal insufficiency, renal transplant, renal nephropathy, preoperative urinary retention, a recent history of more than 3 UTIs per year, a previous history of nitrofurantoin-induced pulmonary injury or nitrofurantoin associated cholestatic jaundice/hepatic dysfunction , known immunocompromised condition (organ transplant, chemotherapy, immune suppression associated with autoimmune disease).

Intervention: Extended release nitrofurantoin 100mg or an identical appearing placebo capsule to be taken daily while using an indwelling catheter or performing CISC.

Primary outcome: The frequency of symptomatic UTIs confirmed with a positive urine culture within 6 weeks of surgery. UTI definition will be culture growth of $\geq 10^3$ colony forming units (cfu)/mL of uropathogenic bacteria in in a single catheter urine specimen or a midstream voided urine specimen and the presence of symptoms or signs compatible with UTI without other identifiable source. This is consistent with the American Urology Infectious Disease Society of America (IDSA) and National Surgical Quality Improvement Program (NSQIP) guidelines, with the exception that postoperative UTI will be diagnosed with a colony count of $>10^3$ instead of $>10^5$ for symptomatic women, given the increased risk in this population.

Secondary outcomes:

1. Frequency of adverse events related to daily nitrofurantoin exposure, primarily nausea, vomiting, headache and flatulence, but including diarrhea, dyspepsia, abdominal pain, constipation, emesis, dizziness, drowsiness, amblyopia, pruritis, urticaria, hair loss, fever, chills, and malaise as well as acute pulmonary, dermatologic or hepatic reactions.
2. Frequency of urine cultures positive for nitrofurantoin-resistant isolates, defined as a single organism of 10^3 or greater colony forming units with resistance (not including intermediate sensitivity) on susceptibility testing.

Protocol in Detail:

Women scheduled for surgical correction of urinary incontinence or prolapse can be introduced to the study pre-operatively in the clinical office or immediately prior to surgery, and will be consented and randomized post-operatively should they fail their voiding trials. Voiding trials may be performed per protocol at the participating institution. At our institution, the bladder is back filled through a Foley catheter with 300cc sterile water. Patients are considered to pass the voiding trial when they spontaneously void with a post-void residual (PVR) that is 100cc or less. Patients who 'fail' a voiding trial are either taught CISC prior to discharge, or are otherwise discharged with an indwelling catheter. A documented PVR of 100cc or greater is preferred for study inclusion.

Screening for study inclusion will be performed at the time of diagnosis of postoperative urinary retention after pelvic reconstructive surgery. Women who agree to potential study participation will be approached by an investigator from the research team. The investigator will review the inclusion/exclusion criteria to determine the patient's eligibility. Informed consent will be reviewed and signed with eligible patients.

At enrollment, baseline clinical data and information on voiding symptoms will be abstracted from the clinical chart or collected when not current within six months (see Enrollment Data Abstraction Sheet).

Study drug and placebo will be prepared by the UPMC investigational drug service and shipped to participating sites. A ten day supply of study drug will be placed in identical pill bottles with labels indicating that they are part of this study and contain either nitrofurantoin 100 mg tabs or placebo, and instructions to take one capsule daily

during catheter use. Study drug and a block randomization log will be provided to participating sites in blocks of 8 patients. When patients are enrolled, they will receive a study ID number from the randomization log and receive the study drug pre-labeled with the study ID number. The pharmacy, investigational drug service, or other personnel of each site will administer the randomization log and provide the participant with study drug at enrollment.

Medication (nitrofurantoin or placebo) will be self-administered by the patient once daily beginning on postoperative day one and continuing each day the patient requires catheterization. Patients who must take a study drug while under hospital care will self-administer study drug with a physician order that they may do so, and under supervision of the nursing staff, or per hospital protocol of participating institutions.

Patients using indwelling catheters will be seen for repeat voiding trial at the discretion of the treating provider. All women will be asked to complete a simple daily diary for each day they use a catheter to document compliance with study drug, symptoms of UTI, or adverse effects from study drug (see Daily Diary). Criteria for discontinuing indwelling catheter use will be passing a voiding trial per policy of participating sites. Criteria for discontinuing CISC will per policy of participating sites. At our institution, patients may discontinue CISC when they are able to void spontaneously with a PVR of less than 100cc on two consecutive voids, and this will be the preferred criteria. Patients will return the diary by mail in pre-addressed envelopes when they discontinue catheter use.

Patients will be strongly encouraged to seek care for possible UTI symptoms from their study physician. A symptom survey and urine specimen for culture will be collected. Catheterized specimens are preferred although clean catch specimens will be accepted. UTI symptoms will be treated with antibiotics (other than Nitrofurantoin) at the discretion of the treating physician; type, duration and strength of antibiotic will be recorded. When symptoms occur outside of business hours, patients may reach an on-call study staff member who can help them facilitate urine culture collection as well as clinical care. Empiric prescription of antibiotics prior to obtaining urine for culture will be strongly discouraged. Patients will be given a prescription and specimen cup for a urine culture so they can drop off a specimen if empiric treatment is necessary. They will also be given a card identifying them as study participants with a request to send a urine culture and to forward results to their physician should they present for care to an outside facility.

An episode of UTI symptoms will only be considered a UTI if confirmed by a positive urine culture, as defined below. If empiric treatment occurs, the episode will be counted as a UTI.

All patients will be seen by a physician and a research staff at a 6-week postoperative visit. At the 6-week visits patients will return their diary if it has not yet been sent in, and return any unused study drug. The study team will review the chart for any adverse events or UTIs not previously reported, and patients will fill out a brief

questionnaire to confirm the same. Duration of catheterization will be confirmed between the patient diary and the patient chart. If the patient is still using an indwelling catheter or performing CISC at the end of the study, we will not break the randomization code until the study is completed. The decision to continue or initiate antibiotics will be made by the patient and her treating physician.

During the six week study period, the central Study Coordinator will track patient participation. They will contact the patient at three to four day intervals to answer any study related questions, confirm patient is filling out the daily diary, and remind patients to return their diary when catheterization is completed. They will remind patients to follow-up six weeks following surgery and to contact their study physician for any UTI symptoms.

The study will end 6 weeks after surgery of the last recruited patient.

DATA COLLECTION

Data will be collected by participating sites using data collection forms (see appendix). All paper forms will be sent via encrypted email to the Data Coordinating Center. Forms will be reviewed for errors and completion by the Study Coordinator and entered into a central database.

CONFIDENTIALITY

Extensive efforts will be made to ensure and maintain participant confidentiality. All identifying information must be maintained in a secure area at all times in accordance with participating site Institutional Review Board policy. When documentation is transferred to the Data Coordinating Center (DCC), data sheets must include the Subject ID number without personal patient identifiers.

Participants will be assigned a Study ID number at study enrollment. Study ID number will be taken from the randomization log provided to the participating sites. This Study ID number should be used label all data collection sheets. All communication between the DCC and participating sites regarding patient data will occur via the Subject ID number. The staff at the DCC will not have access to any identifying information available to the participating site. The DCC staff will have access to the Subject ID number for data management purposes. Once a Subject ID number has been assigned, it should never, for any reason, be reassigned.

The DCC will maintain the randomization log. They will maintain a record of the block randomization including which Study ID numbers have been assigned to which clinical site. Only the onsite pharmacy or other research staff personnel for each clinical site will maintain patient identifiers associated with the Study ID number. This information must be kept in a secure area in accordance with each site's IRB policy and approval.

POWER ANALYSIS

In a study by Rogers et al, the rate of UTIs with placebo in women with suprapubic catheters was 33%. In a study at Magee Womens Hospital, 13% of those performing CISC post-operatively developed a symptomatic UTI, despite daily prophylactic nitrofurantoin (Sutkin, 2010). Assuming a 60% decrease attributable to nitrofurantoin from 33% to 13%, with 80% power and a two-sided alpha of 0.05, we will need 69 patients per arm. Allowing for a 10% dropout rate, we will recruit a total of 154 patients, 77 per arm.

DATA ANALYSIS

Demographics and baseline data will be analyzed by Student's t-test and chi-squared test or Fisher's Exact test as appropriate.

Primary outcome: The frequency of urinary tract infection within 6 weeks of surgery will be analyzed by intention to treat using a chi squared test. This primary outcome includes symptomatic, culture-proven UTI as well as women who were empirically treated outside of protocol. Women who were diagnosed with multiple urinary tract infections during the study period will be counted, but only the first UTI for each patient will be included. A secondary analysis of symptomatic, culture-proven UTIs, excluding those who were empirically treated, will be performed by chi square test. In addition, frequency of urinary tract infection among women undergoing urinary incontinence (UI) surgery only, pelvic organ prolapse (POP) surgery only, or a combination of UI/POP surgeries will be performed using chi squared or Fisher's Exact test as appropriate.

Secondary outcomes:

1. Frequency of adverse events related to daily nitrofurantoin exposure as defined above will be compared with chi-squared test or Fisher's Exact test as appropriate.
2. Frequency of urine cultures positive for nitrofurantoin-resistant isolates will be analyzed by chi-squared test or Fisher's Exact test as appropriate.

PROJECT SCHEDULE:

- February 8, 2016: Final confirmation of participating sites
- February 8 to April 4, 2016: Start up including IRB approval at all sites
- April 2016 until April 2017: Recruitment
- May through July 2017: Data analysis, manuscript completion

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