Study Title: Betadine vs Sterile Water for Periurethral Preparation Prior to Straight Catherization in the Clinic Setting: A Randomized Controlled Trial

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Research Protocol

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Background/Objectives:

Clean intermittent self catherization (CISC) is a well-established method of management of incomplete bladder emptying that has been utilized for the last 50 years [1]. This technique has been used in the longterm management of patients with neurogenic bladder and has been studied in spinal cord injury patients specifically proving to be safe and effective [2,3]. Short term CISC or indwelling catheter use is necessitated in up to 50% of women following Urogynecologic procedures due to development of temporary voiding dysfunction [4,5]. Current teaching for patients on use of CISC as outlined by the American Urogynecologic Society includes hand washing, followed by use of sterile lubricant and insertion followed by removal of the catheter after completion of emptying [6]. Catherization in the clinical/office setting is conventionally accompanied by the use of antiseptic solution applied to the periurethral area, commonly 10% povidone iodine or chlorhexidine [7]. Catheter associated urinary tract infections (CAUTI) have long been a CDC metric for tracking infectious disease prevention and has in years past been the leading cause of nosocomial infection. Current data (Jan 2024) suggests that CAUTI is now the 5th cause of nosocomial infection in the US [8,9]. Current guidelines for CAUTI prevention do not recommend specific periurethral/meatal cleansing practices and states that there is currently insufficient evidence to prove that meatal cleansing reduces CAUTI [10]. The role of chemical antiseptics in periurethral preparation/cleansing have been challenged in both the hospital and home settings by randomized controlled trials completed in the fields of pediatrics, obstetrics and assisted living. These studies have demonstrated no statistically significant differences in incidence of UTI or positive urine cultures (as defined by differing criteria for each study) when comparing use of sterile water to povidone iodine or chlorhexidine for periurethral preparation [7,11,12]. However, data from these studies is limited to specific populations not distinctly similar to that of a typical Urogyecology practice and 2 out of 3 studies utilized indwelling catheters rather than straight catherization.

Aside from the debate on utility of povidone iodine or chlorhexidine for UTI prevention there is the matter of associated risks of use of these agents. Chemical antiseptics have been associated with increased patient discomfort at the time of catherization and even

microtrauma to the periurethral area [13]. Povidone Iodine carries an approximate 3% risk of skin irritation with reported incidence of true allergies being much lower at approximately 0.4%, anaphylaxis has been reported with vaginal topical application of Povidone Iodine [14,15].

The objectives of this proposed study are as follows:

1. Demonstrate similar rates of bacteruria following minor in office procedures with topical application of 10% Povidone Iodine and sterile water for periurethral preparation
2. Determine whether there is a clinically significant difference in patient discomfort with the application of 10% Povidone Iodine when compared with topical application of sterile water at the time of in office straight catherization

Study Design/Methodology:

Study Design: Randomized controlled trial

Inclusion Criteria: Aged 18+, Patient undergoing in office straight catherization

Exclusion Criteria: History of culture proven recurrent UTI (2 in any 6-month period or 3 in any 12-month period), Urine Analysis with +Nitrites, Catherization for any reason in the last 4 weeks, History of Iodine allergy, Patients unable to speak English or does not have the capacity to consent. 2-3rd trimester pregnancy.

Intervention: Application of 3 swabs of 10% Povidone Iodine to the periurethral area prior to straight catherization with a flexible catheter coated with sterile lubricant without lidocaine (as is current standard practice in our office) vs application of 3 swabs of sterile water to the periurethral area prior to straight catherization with a flexible catheter coated with sterile lubricant without lidocaine

Randomization: Computer generated, 1:1 based on procedure being performed in clinic as high risk (Cystoscopy, Urodynamics, Bladder Instillation) and low risk (Post Void Residual Straight Catherization). From this randomization list we will create sealed envelopes to be opened at the time of in office intervention.

Blinding: Patient blinding to intervention of application of 10% Povidone Iodine vs Sterile Water

Sample size: 148 (74 per group) based on 80% power to demonstrate noninferiority with a noninferiority limit of 10% and an estimate 20% lost-to-follow-up rate. This was determined the non-inferiority sample size calculator at https://www.sealedenvelope.com/power/binary-noninferior/. We assume 95% of patients will be infection free in both the Povidone Iodine and Sterile Water groups, and we consider a 10% non-inferiority limit. To achieve the desired power, this requires 59 patients providing data from each group. Due to an anticipate 20% dropout rate from catherization to the follow-up appointment where the primary outcome of UTI is measured, we plan to randomize 74 patients to each group, so that we expect to achieve the sample size target.

Participant Recruitment Methods:

The potential participant pool will include patients seen at the Springs Urogynecology Clinic by Dr. Stacy Lenger, Dr. Sean Francis, APRN Claire Hagan and APRN Alyce Goodman Abraham as well as patients seen at the Mary and Elizabeth Urogynecology Clinic by Dr. Ankita Gupta and APRN Carrie Thonen. Established patients will be initially contacted by phone in the week leading up to scheduled appointments in which the clinical evaluation and or treatment plan will require in office catherization. The initial contact phone call will include a basic description of the study and gage patient interest. If patients report interest in participation patients will be asked to arrive early for their upcoming appointment at which time they will be provided with a recruitment handout and opportunity to review this document and ask the provider and or study representative, which may include current Urogynecology fellows, questions related to the study. Patients will then be asked if they would like to participate in this study, if so they will be provided with informed consent documents. New patients will be asked at the time of their visit, if their new patient visit involves catheterization, if they would like to participate in the study. Patients will be eligible to participate in the study more than once as long as instances of catherization are more than 4 weeks apart and they continue to meet the listed inclusion criteria. They would be consented before every encounter.

Informed Consent: If at the time of patients scheduled appointment, they report interest in participation in this study they will be provided with informed consent documents. There will be no waiting period from time of informed consent and study participation.

Research Procedures: The department of Urogynecology Clinic schedule will be screened by research team members weekly to identify patients that meet study inclusion criteria as above. Patients who meet inclusion criteria will be contacted by telephone by research team members and provided with a reminder regarding their upcoming appointment and will be briefly educated about the existence of this study and screened for interest. If patients report interest, they will be asked to arrive 15 minutes prior to their scheduled appointment, notify front desk staff that they are interested in participation in this study.

On the day of the patient's scheduled appointment, on arrival they will be provided with the recruitment handout for review and complete informed consent if they desire to proceed with participation in the study. Prior to their clinical encounter patients will be asked to complete an Acute Cystitis Symptom Score (ACSS) Questionnaire as well as Charlson Comorbidity Index. As part of the standard rooming process in our clinics patients will be asked to provide a urine sample prior to the initiation of their clinical visit. These samples will undergo urine point of care dip and be screened for evidence of urinary tract infection. If Nitrites are present on dip analysis patients will be excluded from the study. The patients that still meet inclusion criteria at this point will then be randomized to the sterile water group or betadine group using a computer generated 1:1 system stratified by procedure being performed. At that time participant ID will be generated and added to protected key spreadsheet. The research staff member will then provide the provider with a sealed envelope containing the group assignment.

The patient room will be set up with standard catherization equipment including a sterile catheter, single packet of sterile lubricant, gloves as well as both, 10% povidine iodine or sterile water. Based on patient group assignment the provider will use either 3 swabs of 10% povidine iodine or 3 swabs of sterile water for use in periurethral cleansing. This will be performed at the pelvis under the drape as is our usual protocol to allow for blinding.

At the time of catherization, with patient in recumbent or supine position the pelvis will be draped. Proper hand hygiene will be performed, and gloves donned. Sterile lubricant without lidocaine will then be applied to the catheter and the periurethral area will be cleansed with the 3 swabs specific to the patients assigned group. Cleansing procedure will be standardized to include 3 swipes of the cleansing liquid. Each swab is used once with cleansing swipes from anterior to posterior. Following cleansing catherization will be performed with lubricated catheter. At this time patients may undergo additional evaluation and or treatment based on the intended purpose of their catherization including Urodynamic testing, bladder instillation, cystoscopy or evaluation of post void residual.

At the conclusion of the patients encounter they will be asked to rate their pain or discomfort at the time of catherization on a visual analog pain scale (VAS). Patients will

then be provided with a follow up reminder to present within 2 weeks for repeat urine sample collection and repeat ACSS. If patients are not able to physically present to clinic over the 2 week follow up period, they will be provided with a lab slip for urinalysis collection at the lab of their choice, release of records form and an ACSS Questionnaire to complete within the 2 week period.

For purposes of follow up patients may present at any time over the course of the subsequent 2 weeks and provide a urine sample as well as complete an ACSS questionnaire. Patients will present to the office and notify front desk staff that they are participants in this study here for follow up urine sample.

We will attempt to make this 2-week visit coincide with scheduled appointments for patients. Investigators will also record if patients presented to or contacted the office prior to 2 weeks with symptoms of a UTI and results of urine cultures, if sent.

All urine samples collected over the course of this study will be reviewed by research staff and patients notified by telephone and treated for diagnosed infections. Results will be reviewed weekly. Urinalysis results, ACSS questionnaire score and VAS scores will be complied in RedCap for later statistical analysis.

Minimizing Risk: Regarding patient data, all patients will be assigned a participant ID at the time of randomization which will be used to compile data in a deidentified manner in RedCap. A key containing patient MRN corelating with participant ID will be maintained securely on password protected RedCap. Regarding patient health and physical safety interim analysis will be performed, if statistically significant different rates of urinary tract infection are identified the study will be discontinued. Additionally, if unforeseen severe adverse events are reported analysis will be performed to determine if there is a causal link with the study and if this is determined the study will be discontinued.

Plan for Analysis of Results: Summary statistics between the two treatment conditions (Povidone Iodine and Sterile Water) will be computed using means, standard deviations, counts, proportions, etc., as appropriate. Comparisons between these group will be assessed using two-sample t-test for continuous variables and Fisher exact test for binary and categorical variables. The primary outcome of UTI at the two-week follow-up appointment will be compared using a non-inferiority test with a non-inferiority limit of 10%. Analysis of the secondary outcome of VAS pain score will be compared between treatments using a two-sample t-test. We will additionally use regression method to

correlate UTI and VAS pain score with patient demographics and clinical features. Throughout, if normality assumptions are violated, we will use transformations and/or non-parameteric statistical methods. We will use a significance level of alpha=0.05 and, except for the non-inferiority test, all statistical tests will be two-sided. Statistical analysis will be performed using R statistical software.

Research Materials, Records and Privacy: Data to be collected includes a key matching patient MRN with participant ID this is necessary to perform follow up on patient urinalysis results which will result in Epic. This key will be stored in University of Louisville SharePoint, access will be held by Dr. Gupta and Dr. Seymour. Deidentified data will be collected using participant ID in RedCap, this will include patient age, race, BMI, Charlson Comorbidity Index, primary diagnosis for which they are receiving care in Urogynecology clinic, additional procedures undergone at the time of their catherization, time to follow up for second urinalysis in days, urinalysis results, VAS rating, ACSS questionnaires. Demographic data of age, BMI and race will be collected to establish what population of patients the study results can be applied to. Clinical data including Charlson Comorbidity Index, ACSS questionnaires, primary urogynecologic diagnosis, additional procedures and time to follow up will allow for further conclusions to be made regarding reasoning for discrepancy in VAS scores and instances of bacteruria. Urinalysis results and VAS scores will be collected for the purposes of primary and secondary outcome measures. All data will be maintained in RedCap with access to the Key held by Dr. Seymour and Dr. Gupta. Deidentified RedCap data access will be given to research team members which will include Urogynecology fellows, OBGYN residents and medical students.

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