TITLE: Tamsulosin vs Placebo to Prevent Postoperative Urinary Retention in Female Pelvic Reconstructive Surgery

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BACKGROUND:

Postoperative urinary retention (POUR) is a well-known risk of surgery, and is particularly common in urogynecologic surgery. While acute POUR has a high rate of eventual resolution after discharge home with a catheter for 5-7 days, this is uncomfortable and inconvenient for the patient, increases the likelihood of urinary tract infection, and increases healthcare costs. In patient surveys, being discharged home from the hospital with a catheter is considered to be a surgical complication, and is rated as one of the worst potential aspects of surgery. Reported rates of POUR in urogynecologic surgery are variable, ranging from to 21-50% (1, 2, 3). In our practice the rate is estimated to be around 30%. Risk factors for developing POUR in this population have been identified, most notably high grade cystocele, higher intra-operative blood loss, urinary retention prior to surgery, and early removal of foley catheter in elderly patients (1, 2). The etiology for POUR is not completely understood, but multiple factors are suspected to play a role including postoperative pain resulting in impaired relaxation of pelvic floor muscles, decreased bladder detrusor muscle contraction, and involuntary contraction of the external urethral sphincter secondary to pain, trauma, or inflammation (4).

Research has not provided a means to prevent POUR in this patient population. One therapy that has been studied in other fields is use of an alpha receptor antagonist (most commonly tamsulosin), with the goal of relaxing musculature in the bladder neck and urethra. The bladder neck and female urethra are known to express alpha receptors. Inhibition of these receptions causes relaxation of muscle in the bladder neck and urethral sphincter, decreasing urethral pressure. Studies of alpha blockade have shown decreased mean and maximal urethral pressure 6 hours after administration of 0.4mg tamsulosin in women with lower urinary tract symptoms (5), and increased mean urinary flow rate and lower urinary tract symptoms after daily tamsulosin for one month (6). Metaanalysis and systematic review of over 700 women receiving tamsulosin reveals improvement in lower urinary tract symptoms in patients with dysfunctional voiding (7)

Tamsulosin has been studied in other surgical fields to decrease POUR. Medani et al studied men undergoing urologic surgery including varicocelectomy, inguinal herniorrhaphy, and scrotal surgery, and randomized patients to placebo versus tamsulosin 0.4mg at 14 and 2 hours before surgery, and 10 hours after surgery. They observed a decrease in POUR from 21.1% to 5.9% (8). A similar study of patients undergoing urologic surgery under spinal anesthesia randomized patients to tamsulosin vs alfuzosin vs placebo, and saw an improvement in the rates of POUR with both alpha antagonists compared to placebo, but no difference between the two alpha-blockers (9). A retrospective review of patients undergoing colorectal surgery revealed that patients who received perioperative tamsulosin for 3 days prior to surgery and after surgery were significantly less likely to experience urinary retention (6.7% vs 25%) (10). In a small, retrospective study of our own patients, tamsulosin use was associated with a significantly lower rate of POUR (OR 0.11, p=0.03).

Development of POUR is of significant consequence to patient health and well-being, as well as to healthcare costs. The risk of POUR in patients undergoing female pelvic reconstructive surgery is high. Risk factors for POUR in this field have been identified, but there are no available prevention strategies. Tamsulosin has been studied in other surgical fields and has been shown to be beneficial to preventing POUR. Determining if tamsulosin is beneficial in preventing POUR in female pelvic reconstructive surgery is a significant step in improving healthcare in this field.

PURPOSE/HYPOTHESIS

The purpose of this study is to determine if perioperative use of tamsulosin decreases the risk of postoperative urinary retention after urogynecologic surgery.

Study aim 1: Compare the rates of passage of initial postoperative voiding trial.

Study aim 2: Compare the rates of any required bladder catheterization in the postoperative period

Study aim 3: Compare rates of UTI in the postoperative period

Hypothesis: Participants who have received perioperative Tamsulosin will have lower rates of postoperative urinary retention following urogynecologic surgery compared to patients who have received placebo.

DESIGN: Randomized Controlled Trial.

SETTINGS: Two large academic Institutions.

EXPERIMENTAL DESIGN AND METHODS:

This will be a multi-institutional randomized controlled trial. Written consents explicitly explaining the risks and benefits of the study will be obtained from the patients.

The **inclusion** criteria are the following:

-Patients must be 18 years or older as well as willing and able to provide informed consent

-Patients must be undergoing a scheduled surgery for pelvic organ prolapse or urinary incontinence

-Standard postoperative plan must include admission to the hospital with foley catheterization overnight the night after surgery, and planned removal of foley catheter and active voiding trial on postoperative day 1.

The **exclusion** criteria are the following:

-Patient unable or unwilling to provide informed consent

-Severe allergy to sulfa drugs

-Known allergy to tamsulosin or another alpha antagonist medication

-History of urinary retention

-Planned bladder catheterization greater than 24 hours after surgery

-Known untreated UTI prior to surgery

-Current use of alpha antagonist medication for hypertension

-End stage renal or liver disease

Procedures

-Once patients are enrolled and consents are obtained, they will be randomized into either tamsulosin or placebo group

-Investigational drug services will provide medication to the study investigators who will provide patients with their medication at the preoperative visit, which is typically 1-2 weeks prior to surgery.

-Patients will be instructed to take one pill by mouth daily for three days prior to surgery.

-While hospitalized after surgery, patients will continue to take their study medication. They will take one extra pill the morning after surgery, 3-4 hours prior to their voiding trial. Other than this one extra dose, they will continue taking one pill every evening after dinner until their medication has run out. This will total 3 days prior, and 6 days after surgery.

-The voiding trial, which is standard practice after urogynecologic surgery, will be performed the morning after surgery. This will include filling the bladder with 300cc of normal saline or sterile water retrograde through the foley catheter, then removing the catheter. The patient will have 15 minutes to void. The volume of their void will be measured. If they void 200ml or greater, they have passed the voiding trial. If they void less than 200ml or cannot void at all, they have failed the voiding trial and the catheter is reinserted with plans to remove it in the office in 4-6 days. If the void is not measured or cannot be measured for any reason, an ultrasound of the bladder will be performed to determine the post-void residual volume in the bladder with a threshold of must void 2/3 of instilled volume.

-The patient will complete the Voiding Symptom Survey at time of enrollment and again on postoperative day 4. They will be provided with a copy of this form prior to their discharge from the hospital. They will be contacted via telephone to report their results.

-Data collected will include: Study number, MRN, age, race, BMI, current tobacco use, parity, ASA class, preoperative history of urinary retention, preoperative prescription for medication for overactive bladder or urge incontinence, urodynamic testing results (presence of stress urinary incontinence and detrusor activity, increased EMG recruitment, post-void residual, peak flow rate, detrusor pressure at peak flow rate), preoperative diagnosis particularly of stress urinary incontinence or pelvic organ prolapse, surgery performed, surgical complications, estimated blood loss, voiding trial results, presence of POUR, time until resolution of POUR, presence of postoperative urinary tract infection, results of postoperative Voiding Symptom Survey.

Data security

-Study data will be collected and managed using REDCap electronic data capture tools. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Identifiable information will be stored in password protected directory accessible only by study personnel. Finally, no identifiable information with be shared outside of our institution and all non-identifiable information will be pooled and released as a group for the final study after statistical analysis is complete. After the completion of the statistical analysis phase and a sufficient length of time, the file containing the patients' MRNs and study specific unique numerical identifiers will be deleted. Patient MRN and unique study specific identifier will be kept until completion of data analysis or >2 years, whichever is greater. The file containing study specific identifier and other study, as well as pooled statistics data, will be kept for a period of greater than 3 years per policy to allow additional statistical analysis as may be required for final manuscript revisions. Every attempt to obtain and maintain a complete and thorough record of data points will be made by the study staff. In the event that any data is unable to be obtained from the usual protocol source, every attempt to obtain the data from additional electronic medical record sources will be made. If no data is obtainable, said data point will not be placed in statistical analysis and reported as such.

No paper records will be kept other than the consent forms which will be kept in a locked cabinet in a locked office

Data and Safety Monitoring

-Data and safety monitoring will be performed by the primary investigators throughout the study to ensure all above policies are being followed. Upon receipt of the study drug, patients will be reminded of contact information to reach investigators with any questions or concerns. They will be monitored closely in the hospital for any abnormalities which is standard for perioperative care. Investigators will again address any questions or concerns during the scheduled postoperative telephone follow up to discuss the questionnaire. The primary investigators will meet monthly to review patient enrollment and potential adverse events. Any unexpected or significant adverse event may prompt a preliminary statistical analysis and/or immediate halt in enrollment or cancellation of the study.

-<u>Safety monitoring/event reporting</u>: study investigators will actively monitor for unanticipated problems, adverse events, or protocol deviations, with specific emphasis on any events involving risk to subject or others. Record of these events will be kept in the Safety Monitoring Log. Monitoring will take place during preoperative communication with patient, during hospital stay, at the follow-up phone call, and in the postoperative period. In addition to monitoring and record keeping, events will be reported as appropriate. Unanticipated problems and any adverse events that may change the risk/benefit ratio will be reported to the IRB within 3 days of discovery per institutional guidelines. Serious adverse events will be immediately reported to the IRB and the patient's primary provider as soon as investigator is aware of the incident. Any adverse events that are felt to alter the risk/benefit ratio of the study may prompt a review and revision of study protocol and/or consent form. Non-serious adverse events will be kept in the Safety Monitoring Log.

Statistical considerations

-Data will be evaluated with descriptive statistics, including means, medians, standard deviations, and ranges. Comparisons between the experimental and control group will be evaluated with univariate and multivariate logistic regression as appropriate. A conservative power analysis was performed and determined that a total of 118 (59 in each arm) would be required to achieve a power of 80% with an alpha error of 0.05 in order to detect a decrease in the rate of failed void trial from 30% to 10%. To account for a 15% dropout rate we will recruit 136 participants.

OUTCOMES:

PRIMARY OUTCOME: pass/fail of voiding trial on the morning after surgery

SECONDARY OUTCOMES: development of POUR at any time after surgery, diagnosis of urinary tract infection after surgery, Voiding Symptom Survey score

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