Department of Urology

Prophylactic Tamsulosin Use for Prevention of Post-Operative Urinary Retention

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1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

Primary Aim

- The primary outcome of this study is to assess how the prophylactic administration of tamsulosin affects the rate of post-operative urinary retention (POUR) for a select group of surgical procedures

Secondary Aims

- The secondary outcomes include:
  - Assess the relationship between I-PSS score and likelihood of POUR in treatment and control groups
  - Assess post-operative post-void residual volumes between groups

1.2. Background

Post-operative urinary retention (POUR) remains one of the most common surgical complications encountered. Rates of POUR remain variable in the current literature with rates between 3% [1] and 41%[2] (Peterson, et al) reported.

Tamsulosin is a common medication used in patients with urinary retention and lower urinary tract symptoms. It works by blocking alpha receptors in the prostate and bladder neck allowing for improved outflow of urine. Fortunately tamsulosin is quite safe, is well-tolerated by patients, and has few side effects. The use of tamsulosin for POUR is currently not given until urinary retention is diagnosed. However there is emerging evidence that tamsulosin may have prophylactic properties against POUR. In one placebo-controlled trial, prophylactically administered tamsulosin was shown to significantly reduce the rates of urinary retention after inguinal herniorrhaphy from 15% to 25% when administered 6 hours prior to surgery[3]. Interestingly, with a half-life of approximately 14 hours, tamsulosin would not achieve steady state concentrations within such a short time frame. Similarly, Madani, et al showed a reduction in POUR rates from 21.1% to 5.9% when tamsulosin was administered 14 and 2 hours prior to inguinal or scrotal surgery.[4] POUR is often multifactorial in nature. However, there are known risk factors for urinary retention including age, gender, and previous episodes of urinary retention.

2. STUDY DESIGN

2.1. Overview

This randomized open-label study will be comprised of 2 cohorts: one control group and one treatment group. The trial will be conducted as an open label randomized trial to evaluate the efficacy of tamsulosin in the prevention of post-operative urinary retention. The study will include pre- and post-surgical evaluations of patients including symptoms of urinary retention and any adverse effects contributable to the study medication.

2.2. Rationale for Study Design

Granted that a placebo-controlled trial would be a more powerful study, the complex issues of acquiring and distributing a placebo for a generic medication have led to the above described non-placebo controlled design.

2.3. Rationale for Dosage

Standard dosing for tamsulosin is 0.4mg administered orally. Tamsulosin is typically administered once daily in the evening as recommended by the manufacturer. Three doses was the prescribed pre-surgical treatment regimen based on the known half-life of tamsulosin being 14 hours. As such, 3 doses will allow for >5 half-lives of the medication at therapeutic dosing to achieve a therapeutic steady state. Tamsulosin has been proven to be well tolerated by elderly populations.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) Number of Subjects:

A total of 160 subjects will be enrolled in this study (80 within the control group (no tamsulosin) and 80 within the treatment group (receive tamsulosin).

b) Gender and Age of Subjects:

Only males age 40 years and older will be included in this study. Males alone will be selected due to the fact that tamsulosin and its role in urinary retention have been best proven and most reliably useful in males. This age was selected because older males are considered at highest risk of POUR.

c) Racial and Ethnic Origin:

There will be no racial or ethnic restrictions for participation.

d) Vulnerable Subjects:

There will be no vulnerable subjects included in this study.

3.2. Inclusion and Exclusion Criteria

a) Inclusion Criteria:

- Any male age 40 or older
- Scheduled to undergo one of the planned surgeries (thoracic, general, or urologic)
- Ability to give informed consent
- Willing to participate in the study
- Any racial or ethnic origin

b) Exclusion Criteria:

- Current use of alpha blocker
- Current use of a strong CYP 3A4 inhibitors
- Any allergy to tamsulosin, alpha-blocker medication class, or anaphylaxis allergy to sulfate containing medications
- Patients with any upcoming surgery for cataracts
- Currently enrolled in a clinical trial
- Inability to give informed consent

3.3. Discussion of Subject Population

Patients with upcoming cataract surgery will be excluded due to the known floppy iris syndrome associated with tamsulosin administration. Those with a severe reaction to sulfa drugs will be excluded due to a known, but relatively uncommon cross-sensitivity between tamsulosin and sulfa drugs.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method of Subject Identification And Recruitment

Patients of the investigators listed in this protocol (thoracic, surgery, urology), who have been identified as appropriate for the above listed procedures and who meet inclusion/exclusion criteria, will be offered the option to enroll in this study. This will occur at the time of in-office surgical consultation for the proposed procedure. Subjects will be recruited from and surgeries will be performed at both SMH and HH. This study will receive Highland Hospital approval prior to enrolling subjects.

4.2. Process of Consent

The care provider who will see the patient for the in-office surgical consultation will offer participation if the patient meets inclusion/exclusion criteria. Eligible subjects will be allowed to take a copy of the consent form home for review. The care provider will ask the patient if they would like to be contacted about the study from a research team member. If the patient agrees to be contacted, the care provider will forward the patient's contact information to the team member. The team member will contact the patient to check interest in participation and answer any questions. If they choose to enroll in the study, a visit will be scheduled and consent will be obtained by a member of the research team. Study objectives, procedures, potential risks, benefits and alternatives (such as not to participate) will be discussed. Patients will be reminded that they can elect not to participate without risking loss of present care they would otherwise expect to receive. Research interventions vs standard of care interventions will be clearly stated to the patient during the consenting process. A copy of the signed consent form will be given to the subject and the original consent form will be placed in the research record. Consent will be obtained in a private place with a closed door to ensure privacy.

5. METHODS AND STUDY PROCEDURES

Eligible subjects who agree to participate will be randomized to one of the following two groups:

1. Control Group
   Subjects in the control group will undergo the planned general, urologic, or thoracic surgery procedure and receive no tamsulosin, but will receive education about the signs and symptoms of urinary retention.

2. Treatment Group – patients who are to undergo the following surgeries will be included in this group:

   - Open inguinal herniorrhaphy
   - Inguinal orchiectomy
   - Transscrotal hydrocelectomy
   - Transscrotal spermatocelectomy
   - Laparoscopic cholecystectomy
   - Laparoscopic Nissen fundoplication
   - Laparoscopic paraesophageal hernia repair
   - Thoracoscopy

   Subjects will receive education about the signs and symptoms of urinary retention

   Once identified by participating surgeons as potentially eligible to participate in the study, patients will be directed to a study team member who will review and confirm study eligibility, obtain consent, medical history, demographic information, concomitant medications, randomization, and distribution of medication (if applicable).

   Control Group
   Subjects in the control group will receive education about the signs and symptoms of urinary retention.

   Treatment Group
   Subjects in the treatment group will be called 3 days prior to their scheduled procedure. During this telephone encounter, subjects will be reminded to initiate the study medication (1 dose each night for 3 consecutive nights prior to surgery). Also, subjects will receive education on the signs and symptoms of urinary retention.

   All subjects will complete the International Prostate Symptom Score (I-PSS) voiding symptom score index (Appendix 2). Subjects will be asked to complete this standard of care validated questionnaire prior to surgery (at the time consent is obtained) and during the post-op telephone contact (research procedure).

Completion of the I-PSS questionnaire will not be considered compulsory for inclusion as the score will be used for comparison of groups and not a measurement of primary outcome.

All subjects will undergo post-void residual (PVR) bladder volume monitoring using an ultrasound bladder scanner prior to surgery to assess baseline voiding. Preoperative bladder scanning will be considered an investigational procedure done specifically for the purposes of the study. At this time, subjects randomized to take tamsulosin will be interviewed regarding any adverse effects noted since initiating the study medication. Responses will be documented on a study-specific form, along with PVR results. This form will be incorporated into the subject's study file. Subjects will then undergo routine perioperative cares per indicated procedure. Following surgery, subjects will be monitored for ability to void. Subjects who undergo procedures that typically involve bladder catheterization will have urinary catheters removed at 12 hours post procedure. Subjects undergoing same-day surgeries will be required to void prior to discharge with measurement of a PVR. Routine PVR measurement before surgery and after surgery if a patient is able to void is not considered standard of care in the absence of urinary retention symptoms and will be a considered a non-invasive research procedure. PVR measurement at the included institutions is not a billed procedure and will not produce any expense for the participating subjects.

Urinary retention will be defined as discomfort with the sensation of a full bladder and a bladder volume >500ml by ultrasonic bladder scan or straight catheterization for discomfort secondary to bladder distention.

All subjects in the treatment group will continue tamsulosin for 2 doses after a successful void. A study team member will call the subject within a week of their surgery to assess for any adverse reactions and to check compliance with the study drug.

Subjects with failure to void will have straight catheterization performed once and a trial of voiding will be reinitiated. A second failure to void will prompt the insertion of an indwelling Foley catheterization for a period of 3-5 days prior to an attempt to void. Both of these procedures are considered standard of care practices. A prescription for tamsulosin will be given to both treatment and control groups for 28 additional days for failure to void (a standard of care practice).

Patients who require outpatient follow-up will have an appointment made with the on-call urologist or urologist's midlevel provider for that day per the standard practices of our institution. Continuation of tamsulosin will be at the discretion of the urologist with whom the patient follows up.

A Schedule of Activities can be found in Appendix 1.

5.1. Treatment Dosage and Administration

Those subjects randomized into a treatment arm undergoing planned outpatient procedures will receive 0.4mg tamsulosin by mouth nightly for 3 doses prior to the day of surgery and for 2 doses following surgery, medication education, and education about signs and symptoms of urinary retention. Subjects will be given a package of 5 tablets of tamsulosin prior to their surgery at the time of consent and randomization. The package will be appropriately labeled to include the research study name, study medication name, instructions on how/when to take the study medication, and study team contact information. Study medication will be provided via the UR Pharmacy. It will be ordered, purchased and distributed by the Department of Urology at no cost to the subject. Compliance with medication usage will be assessed via verbal confirmation the morning of the scheduled surgery and at the post-op telephone contact. This will be documented by the study team member and included in written form within the subject's file. Study medication will be stored in a locked cabinet and only accessed by the study team to be distributed to those subjects randomized to treatment groups at the time informed consent is obtained.

Subjects undergoing planned inpatient procedures will bring their remaining 2 doses to the hospital with them. Per hospital policies regarding home medications, the tablets will be sent to the inpatient pharmacy for verification and distributed to the patient by the nursing staff of the unit to which they are admitted. An order will be placed by the admitting team for Tamsulosin 0.4mg to be taken nightly. Should a subject be unexpectedly admitted following a same-day, outpatient procedure, it will be requested that the subject's arranged ride (as patients are not allowed to drive themselves home after procedures) bring the remaining tablets to the patient. Should no individual be available to deliver the tablets to the subject, Benjamin Nelson, MD (sub-investigator) will be contacted, and 2 tablets will be supplied from the study supply of medication and delivered to the subject's unit.

5.2. Efficacy Assessments

The I-PSS prostate symptom score index will be used to assess preoperative prostatism symptoms. This is an internationally recognized questionnaire for the assessment of prostate-related voiding complaints (Appendix 2).

Pre and post-operative bladder volumes will be assessed using an ultrasound bladder scanner. This will be accomplished by the perioperative nursing staff. This is a standard of care measurement devised for assessing bladder volumes. The use of such

a machine is part of basic nursing care training. Documentation of each bladder scan assessment will be incorporated into the subject's research profile. Urinary retention will be defined as discomfort with the sensation of a full bladder and a bladder volume >500ml by ultrasonic bladder scan or straight catheterization for discomfort secondary to bladder distention.

Compliance with medication usage will be assessed via verbal confirmation the morning of the scheduled surgery at the post-op telephone encounter. This will be documented by the study team member and included in written form within the subject's file.

5.3. Safety Assessments

Medical history and basic physical exam will be performed as part of the standard preoperative work-up. Medication lists will be confirmed at each encounter per hospital policies. Bladder volumes will be assessed using a standard ultrasound bladder scanner. Use of this machine is standard nursing practice and imparts no added risk to the subjects. Failure to void will be managed per standard post-operative policies with a trial of sterile straight catheterization for the first episode of urinary retention. Any subsequent inability to void will be managed with a sterilely placed indwelling Foley catheter for a period of 3-5 days prior to an attempt to void. Both of these procedures are considered standard of care practices. A prescription for tamsulosin to be filled with the subject's discharge prescriptions will be given to both treatment and control groups for 28 days for failure to void (a standard of care practice).

5.4. Assessment of Subject Compliance

Confirmation of study medication adherence will be verbally assessed by a study team member and documented in the subject's research record.

5.5. Costs to the Subject

There are no costs to the subject for their participation in this study. The Department of Urology will provide study medication to subjects assigned to the treatment arm.

5.6. Payment for Participation

Subjects will not receive financial reimbursement for participation in this study. A parking pass will be given at the first visit.

5.7. Return of Individual Research Results

Subjects will be informed of bladder volumes at the time of bladder scanning. All other research results will be evident to the subjects based on the nature of the study as they will be aware of the presence or absence of urinary retention.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Concomitant use of other alpha-blockers will be disallowed and part of the exclusion criteria for this study. Those subjects who take medications considered strong CYP 3A4 inhibitors will also be excluded.

7. SUBJECT WITHDRAWALS

Subjects will be withdrawn from the study if they:

- Experience an adverse reaction to the study medication
- Elect to withdraw from the study voluntarily

Subjects who have been withdrawn from the study will not be replaced as a predicted 10% drop-out rate has been included in the sample size calculations.

8. STUDY DRUG / DEVICE / BIOLOGIC ADMINISTRATION / ASSIGNMENT

8.1. Study Drug/Device/Biologic

- Tamsulosin

8.2. Dosage of Study Drug/Biologic

- Tamsulosin 0.4mg oral tablet every night x 5 (3 days prior to surgery and 2 days following surgery)

8.3. Subject Enrollment/Randomization

Subjects will be randomized to a treatment or control group using a computerized randomization tool based on the order in which subjects are enrolled.

8.4. Accountability of Investigational Supplies

Study medication will be stored in a locked cabinet and only accessed by the study team. Study medication will be distributed to the subjects directly by the study team. Any returned medication will be documented within the study subject's research record and disposed of according to the research pharmacy recommendations.

8.5. Subject Withdrawal of Study Drug

Subjects who withdraw from the study will not be eligible to continue to be followed in the study.

8.6. Emergency Drug Disclosure

As this is not a blinded study, emergency drug disclosure does not apply.

9. SAFETY AND REPORTABLE EVENTS

9.1. Adverse Event Definition

An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study intervention/drug.

9.2. Serious Adverse Event Definition

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage

9.3. Recording Adverse Events

An adverse event log will be maintained for the duration of the study. The study team will assess adverse events by observation by the investigator, clinical findings, and all voluntary complaints of the subject and will be recorded in the subject's research record.

In the case of an adverse event, the subject will be monitored and managed at the time of the event by the study team and documented in the subject chart. Each adverse event will include a brief description of the experience, the date of onset, date of resolution, duration and type of experience, the severity, the relationship to the investigational agent, contributing factors, and any action taken.

Adverse events will be documented from the time of subject consent until their completion or withdrawal from the study. Follow-up of adverse events will include those that are ongoing/unresolved at the time of subject concluding study participation.

9.4. Responsibilities for Reporting Serious Adverse Events

All serious adverse events will be documented on the Adverse Event Log and subject's research chart from the time of signing the consent form to the final study visit or post-op telephone contact. The principal investigator will be notified immediately of any serious adverse events, and subsequently, the RSRB while complying with regulations and RSRB policy regarding the reporting of adverse events.

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks

Known adverse effects of tamsulosin administration include: orthostatic hypotension (0.2%-0.4%), dizziness (up to 15%), headache (up to 19% and similar rate to placebo), ejaculation failure (8-18%), floppy iris syndrome, and very rarely priapism (1 in 50,000)[5]. Allergic-type reactions such as skin rash, urticaria, pruritus, angioedema and respiratory symptoms have been reported in fewer than 1% of those taking tamsulosin.

10.2. Protection Against Risks

To protect subjects from risk, all individuals with a previous adverse reaction to tamsulosin will be excluded from participation in this study. Those who may undergo future cataract surgery will also be excluded due to the risk of floppy iris syndrome. Individuals with a known severe reaction (anaphylaxis) to sulfonamides will be excluded due to known cross-sensitivities. Those taking medications defined by the FDA as strong CYP 3A4 inhibitors will also be excluded.

10.3. Potential Benefits to Subjects

Subjects may benefit due to the potential prevention of POUR and its attendant results including pain/discomfort, infection, and need for prolonged catheterization.

10.4 Alternatives to Participation

There are no alternatives to participation. This study is voluntary and subjects do not have to participate.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

All subjects will be assigned a unique study number and the key will be kept on a password-protected database in a locked office of the study team. Subject data will be restricted to individuals named in this application. All source documents and other printed PHI will be stored and maintained in the locked offices of the study team.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

Bladder scan volumes will be recorded in the subject's medical record. Administration of study medication will be documented in the medical record.

13. DATA ANALYSIS AND MONITORING

13.1. Sample Size Determination

Given the urinary retention rate in a baseline of expected urinary retention of between 15% and 21% in the specified procedures[3,4] , previous studies with tamsulosin have decreased rates of POUR from between 2.5% and 5.9%.[3,4] To detect a 15% difference between the groups, with an alpha of 0.05 and beta of 80%, a total of 142 patients is required; 72 within the control group (no tamsulosin) and 72 within the treatment group (receive tamsulosin.) To account for patient drop-out rate of approximately 10%, a total of 160 subjects will be enrolled (80 subjects in each group.)

13.2. Planned Statistical Analysis

The primary endpoint of straight catheterization incidence will be analyzed with chi-squared. Postoperative PVR will be computed as a continuous variable using a t-test between the control and each treatment group. Data recorded will be I-PSS scores if returned. Incidence of urinary retention, all bladder scan volumes, return to any health care facility for urinary retention, how long urinary retention persisted. Incidence of any drug adverse side effects will also be recorded.

13.3. Data and Safety Monitoring

Because tamsulosin is quite safe, is well-tolerated by patients, and has few side effects, oversight and monitoring of the conduct and progress of the study will occur every 4 months with the Principal Investigator and members of the study team. The Principal Investigator will be notified immediately for all serious adverse events. Adverse events that are not serious will be managed by the study team (in the departments of Urology, Thoracic, and General Surgery) and reported to the Principal Investigator every 4 months, unless otherwise deemed necessary, such as information that may affect the safety or welfare of subjects, as well as the validity and integrity of the data.

14. REFERENCES

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2. Petersen MS, Collins DN, Selakovich WG, Finkbeiner AE. Postoperative urinary retention associated with total hip and total knee arthroplasties. Clin Orthop Relat Res 1991; 269: 102-8

3. Mohammadi-Fallah M, Hamedanchi S; Tayyebi-Azar A. Preventive effect of tamsulosin on postoperative urinary retention. Korean J Urol 2012; 53: 419-423

4. Madani AH, et al. Effectiveness of tamsulosin in prevention of post-operative urinary retention: a randomized double-blind placebo-controlled study. Br J Urol Int 2014; 40: 30-6

5. Lexi-Comp, Inc. (Lexi-Drugs). Lexi-Comp, Inc.; Accesed: March 22, 2015.

APPENDIX 1

Schedule of Activities for Control Group

PROCEDURES	Research Visit	Day of Surgery	Post-op Phone Call
Confirm Eligibility	X		
Obtain Informed Consent	X		
Randomization	X		
Medical History and Demographics	X		
Concomitant Medication Review	X		
Education of Urinary Retention	X		
I-PSS Questionnaire	X		X
Ultrasound Bladder Scan (pre- and post-op)		X	

Schedule of Activities for Treatment Group

PROCEDURES	Research Visit	3 Days Prior to Surgery	Day of Surgery	Post-op Phone Call
Confirm Eligibility	X			
Obtain Informed Consent	X			
Randomization	X			
Medical History and Demographics	X			
Concomitant Medication Review	X		X	
Education of Urinary Retention	X			
I-PSS Questionnaire	X			X
Dispense Study Drug	X			
Study Drug Compliance			X	X
Phone Call (study drug reminder)		X		
Adverse Event Review			X	X
Ultrasound Bladder Scan (pre- and post-op)			X	

APPENDIX 2

See (PDF) I-PSS Questionnaire