Title: **P**ost-**O**perative **U**rinary **R**etention (**POUR**) in Thoracic Surgery Patients Receiving Prophylactic Tamsulosin

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INVESTIGATOR STUDY PLAN

1. TITLE

Post-**O**perative **U**rinary **R**etention (**POUR**) in Thoracic Surgery Patients Receiving Prophylactic Tamsulosin

2. EXTERNAL IRB REVIEW HISTORY*

NA

3. PRIOR APPROVALS:

NA

Conflict of Interest (COI): The investigators have nothing to disclose

Biohazardous Agents: NA

Radiation*:* NA

4. OBJECTIVES*

Post-**O**perative **U**rinary **R**etention (**POUR**) in Thoracic Surgery is a prospective interventional study aiming to test the hypothesis that the prophylactic use of tamsulosin prior to thoracic surgery in high-risk patients leads to reduced rates of POUR. Urinary retention is defined as eight hours without void after Foley catheter removal and symptoms or bladder volume greater than 600cc.

5. BACKGROUND*

Post-operative urinary retention (POUR) is one of the most common post-operative complications encountered by most surgical specialties. The incidence of POUR can vary from five to 70%.[1] POUR associated factors reported in the literature include type of anesthesia, type and duration of surgery, underlying comorbidities, as well as medicines used in perioperative period. The development of POUR can increase the length of hospitalization and lead to significant morbidities such urinary tract infection, detrusor muscle dysfunction, delirium, cardiac arrhythmias among others.[1]

POUR definition in the literature is not homogeneous, and include >200mL by bladder scanner 4 hours post-op, >500mL by bladder scanner 8 hours post-catheter removal, and >600mL by bladder scanner 4 hours after removal of indwelling urinary catheter. [2–4] Urinary retention is defined in the current study as eight hours without void after Foley catheter removal and symptoms or bladder volume greater than 600 cc.

There are a limited number of studies available regarding POUR after thoracic surgery, and among those, the results vary. In addition, there is continued discussion regarding the appropriate time to remove a urinary catheter post-op to prevent or reduce POUR. Early removal increases the risk for urinary retention, but late removal increases the risk for acquiring a catheter-related UTI [5]. Although it is currently mandated to remove the urinary catheter 48 hours post-op, studies have looked at whether they can be removed earlier without increasing the risk for catheterization. Results of the current published studies are conflicting. Chia, et al compared patients who underwent transurethral catheter removal on the first post-op day with those who had removal after discontinuing patient-controlled epidural anesthesia, usually on the third post-op day. Patients in both groups did not require re-catheterization for retention or suffer from catheter-associated UTIs. However, not surprisingly, catheter-induced urethral pain was higher in the group that underwent later removal. The authors therefore concluded that removal of bladder catheter as early as post-op day one is preferable due to no difference in UTIs or re-catherization as well as decreased urethral pain (2009)[6]. Other studies noted that earlier removal did not increase the risk for POUR and subsequent re-catheterization___0 but was associated with decreased risk for UTIs (4,2). On the contrary, Zaouter, et al defined a correlation between early removal and increased POUR and re-catherization [7].

The role of prophylactic tamsulosin administration in prevention of POUR has been investigated across various surgical subspecialties. Results of these studies are also mixed. In patients undergoing urologic procedures including varicocelectomy, inguinal herniorrhaphy, and scrotal surgery, POUR was significantly lower in the group who received tamsulosin (5.9%) compared to the placebo group (21.2%) [8]. However, there was no difference in POUR rates in patients who underwent spinal surgery or colorectal surgery [9,10].

Although there are varying data across studies measuring POUR after thoracic surgery, there are several risk factors that have consistently been identified that predispose patients to increased risk of POUR after thoracic surgery: age above 40 years, male, diabetes, and BPH [11].

The age cutoff is debatable, but in general, it is accepted that older age correlates with numerous types of bladder dysfunction [6]. There are also certain procedures within thoracic surgery that increase the risk. Lung resection surgery resulted in the highest rate of POUR compared to other procedures like sympathicotomies, pleural biopsies, and mediastinal procedures [1]. In a review of all UMass Memorial patients who underwent thoracic surgery in 2019, the group with the highest incidence of POUR consisted of males above the age of 60 who underwent major thoracic resections. The rate in this cohort was as high as 21%. Although tamsulosin was designed and used to treat patients with symptomatic BPH, we would like to study the effect of prophylactic tamsulosin in the group of patients with the highest likelihood to develop POUR in an effort to prevent this complication.

Post-operative urinary retention is a prevalent complication. Patients who undergo thoracic surgery have greater urinary retention rates compared to others. Data on effective methods to reduce the risk of POUR in this high-risk group are limited.

6. INCLUSION AND EXCLUSION CRITERIA*

Inclusion criteria:

- All male patients >=60 years old undergoing inpatient thoracic surgery for major resections.

Exclusion criteria:

- Prisoners
- Adults unable to consent
- End stage renal disease on hemodialysis
- Indwelling urinary catheter
- Child-Pugh class C hepatic failure
- Usage of the following medications prior to surgery: strong CYP 3A4 inhibitors, other alpha-adrenergic blocking agents.

- patients known to be CYP2D6 poor metabolizers
- History of prostatectomy or cystectomy
- Patients with contraindications to tamsulosin and those at high risk for side effects: hypersensitivity to tamsulosin HCl or any component of FLOMAX capsules,[5] hypersensitivity to sulfonamides. History of known glaucoma, hypotension, plan to undergo cataract surgery in the next 2 weeks

7. STUDY-WIDE NUMBER OF SUBJECTS*

NA

8. STUDY-WIDE RECRUITMENT METHODS*

NA

9. STUDY TIMELINES*

The study will be conducted for twenty-four months from July 2021 – December 2023. The study subjects will be enrolled on an ongoing basis and will include all that fulfill the eligibility criteria.

10. STUDY ENDPOINTS*

See #4

11. PROCEDURES INVOLVED*

There will be no randomization process as this is a single arm trial. The patients will first provide consent to the research when they visit the clinic or in an inpatient setting. As part of the screening process, a physician (or physician's assistant or nurse practitioner) will review the patient's medication list for potential drug-drug interactions with tamsulosin, make a clinical decision regarding the safety of study participation, and document that this screening has occurred.

Since visits are being done remotely, study medication will be mailed to the subject's home and a study staff member will call to answer any questions they may have on how to take the medication. Otherwise, the medications will be dispensed in person by IDS to a research coordinator. The research coordinator will then give the medication to the patient at the time of their Pre-surgical evaluation at the Memorial campus anesthesia clinic.

Starting 2 days before surgery, patients will receive 0.4 mg Tamsulosin nightly, then on the day of surgery, 0.4 mg in holding area, and any additional consecutive days if they experience retention, which is the standard of care for all patients that present with POUR. The minimum number of days a subject could be on the study drug is 3. Tamsulosin is FDA approved and is predominantly used to treat the signs and symptoms of benign prostatic hyperplasia.

The data collection includes identification of patient and operation characteristics that correlate with development of POUR. Some of the factors we propose to study include age, operating time, type of surgery, indication for surgery, presence of epidural, development of other postoperative complications. Patients' names will be de-identified with a unique identifier and will be paired with the corresponding MRN. Principal Investigator and research coordinator will have access to those identifiers.

12. DATA AND SPECIMEN BANKING*

NA

13. DATA ANALYSIS AND MANAGEMENT *

Hypothesis: Prophylactic tamsulosin decreases the rate of postoperative urinary retention (POUR) rates in patients undergoing thoracic surgery

• Primary aim: compare the rates of POUR in thoracic surgery patients treated with preop tamsulosin with historic controls.

The rates of POUR for major procedures in UMass Thoracic service in the target population (male over 60 years old) varied from 8.3% to 33.3% over the last 5 years. In the overall thoracic population, this number was in average 8.4% and it varied from 4.3% to 9.3%.

When analyzing all major procedures performed in the 2019, 48 were performed in males over 60 years old, the study target population. The POUR rate was 33.3%. After applying the exclusion criteria on those 48 individuals, we found an exclusion rate of 33.3% where 16 individuals were excluded, 8 for using Flomax prior to surgery and 8 for using one of the following medications: Buproprion Fluconazole, TMP-SMX, Silodosin, Paroxetine Terazosin, Levofloxacin, Prazosin, Fluoxetine, Sildenafil.

The overall POUR rate was 33% and among the 32 eligible individuals, POUR rate was 28%.

Power Calculation

The incidence rate of 28% was used to estimate the possible scenarios of sample and power of analysis presented in **Error! Reference source not found.**.

The number needed to treat is 60 assuming an 80% reduction of POUR with a power of 80%. Assuming the same volume of operations and taking into account the number excluded due to exclusion criteria (33%), and refusal rate of 25%, we expect to accrue 24 patients per year and achieve the number needed to treat (n=60) in 2.5 years.

All patients who fulfill the eligibility criteria and thus may benefit from the intervention (use of Tamsulosin pre-operatively) will be invited to participate in the study. (**Error! Reference source not found.**)

Table 1. Sample calculation and power-analysis in three hypothetical scenarios of varying effects of tamsulosin

	Hypothetical POUR Incidence in Intervention Group (%)	N*	Post-hoc Power estimate (I)
Tamsulosin intervention Group effect 1 (reduction of 50%)	14	150	49.3%
Tamsulosin intervention Group effect 2 (reduction of 80%)	5.6	60	80.4%
Tamsulosin intervention Group effect 3 (reduction of 90%)	2.8	32	80.4%

*N of male over 60 years old that undergo to in-patient procedures (I) https://clincalc.com/stats/SampleSize.aspx

(II) https://jongguri.shinyapps.io/samplepower/

The study selected parameters are:

- Incidence, group historical control 2019 – 28%
- Incidence (expected), intervention with Tamsulosin – 5.6% (reduction of 80% in incidence
- Subjects, group control – 32 individuals
- Subjects, group intervention (expected) -60 individuals
- Alpha - 0.05

It is expected that the population undergoing thoracic services are similar over time and it will be appropriate to use historical controls to compare with the intervention group.

Our analytical plan is to test the proportion of POUR within the study population comparing with the historical controls. The data quality will be monitored by monthly verification of the completeness of the data, missing values and accurateness of the variables collected.

If a statistically significant reduction in POUR rates is observed before the end of the study, the study will stop and Tamsulosin will be adopted as prophylaxis for this high-risk population in thoracic surgery division. If the benefit is not observed with the estimated sample, the study will be reassessed.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects*

We will analyze the patients' outcomes every 2 months and monitor them for possible side effects associated with tamsulosin: hypotension, insomnia, decreased libido, nausea, diarrhea and dizziness.

15. Withdrawal of Subjects Without Their Consent*

NA

16. Risks to Subjects*

The primary risks to the participants include the side effects associated with tamsulosin: hypotension, insomnia, decreased libido, nausea, diarrhea and dizziness.

17. POTENTIAL DIRECT BENEFITS TO SUBJECTS*

The primary direct benefit to the participants includes decreased urinary retention post-operatively, which is one of the most common and uncomfortable complications many patients face. Decreased urinary retention will also decrease the need for potential re-catheterization. It is difficult to accurately predict the probability of this benefit because results vary depending on the type of surgery and pre-operative risks; however, several studies have documented the successes of prophylactic tamsulosin. [1,12–14]

18. VULNERABLE POPULATIONS*

NA

19. MULTI-SITE RESEARCH*

NA

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

NA

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

The dissemination of the research results will be performed through interim reports, presentations for the UMass Memorial Health Care and UMass Medical School health professionals. Scientific abstracts and papers will focus on sharing the results with the scientific community. As a very relevant topic, it is intended to disseminate the results beyond the scientific community, with the appropriate materials and language (flyers and fact sheets) to the policy makers, health care professionals and overall population, including the subjects that took part in the study. Individual results will be shared with the subjects if requested.

22. SETTING

The research will solely take place at UMMHC Memorial Campus.

23. RESOURCES AVAILABLE

In this study, we assemble the following research team: three thoracic surgeons, one of them being the principal investigator (PI); statistician and six research assistants from UMass Medical - medical students, residents, fellows or other healthcare providers pool. The roles will be as follows:

Principal Investigator/thoracic surgeon: Recruit subjects, perform minimally invasive thoracic surgery, and prescribe tamsulosin according to procedures described in section #11. She will also help analyze the data. Five percent of the PI's time will be dedicated to the project. The PI is a fellowship trained thoracic surgeon with a Master's degree in Biostatistics and Patient Oriented Research. She has published many studies focused on surgical patient-oriented outcomes.

Thoracic surgeons (2 other thoracic surgeons in the division of Thoracic Surgery): Recruit subjects. Perform minimally invasive thoracic surgery and prescribe tamsulosin according to procedures described in section #11. Provide preop and post-operative care for patients.

Research assistants: describe the study and consent subjects. Query subjects on potential adverse effects of tamsulosin. Perform data collection that will be supervised by the PI and statistician. They will have CITI training and be a trained University of Massachusetts health care provider, such as nurse, medical student, resident, or fellow.

Statistician and research coordinator: Analyze the data monthly for quality purposes and at the time of study conclusion. Assist in research protocol development and oversee data collection.

24. LOCAL RECRUITMENT METHODS

Potential subjects will be identified and recruited when they visit the clinic, and the thoracic surgeons will ask them permission for the study staff to approach. Each clinician on the study team will only invite their own patients to participate in the study. In addition, inpatients who require the appropriate surgeries will also be identified by thoracic surgeons.

Individuals who are eligible for the research study will be adult men >60 years old who need to undergo some type of thoracic surgery procedure (See #6 for more detailed inclusion criteria). The patients' names and MRN will be recorded electronically, and the patients' names will be replaced by a code. The identifiers will be destroyed after 6 years after the study completion. Identifiers will not be recorded for patients who are ineligible or those who decline to participate.

Recruitment will be done during clinic visit or in UMass Memorial Hospital. Advertisements and other recruitment materials including flyers, emails, and letters will not be utilized. There will be no payments to the subjects.

25. LOCAL NUMBER OF SUBJECTS

Considering the volume of procedures in 2019 of 48 procedures is maintained over time, it is estimate that we will be able to enroll 60 patients within 2.5 years. This sample size would allow detection of 80% reduction in POUR with a power of 80%. This number of subjects considers a refusal rate of 25% and exclusion rate of 33%.

26. CONFIDENTIALITY

The data will be stored electronically at UMass Memorial Healthcare share drive. The patients' names will be coded and paired with the corresponding MRN. All of the staff involved are HIPPA trained and are part of the UMass Memorial Healthcare/UMass Medical School.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Screening for eligibility and discussion of the research will take place when the patients visit the clinic. Patients who enroll prospectively will be asked to provide signed Authorization. For subjects who serve as historical controls, HIPAA waiver of authorizations will be used.

Data will be abstracted by the thoracic surgery data manager in a secure server and stored on the thoracic surgery shared drive password-protected hard drive provided by UMass Memorial Health Care. Any hard copies of data will be stored in a locked office in Thoracic Surgery. The system hosted locally by UMass Memorial Health Care and employs user authentication and role-based security. Web-based data entry is via an SSL cryptographic transport protocol. Additional

security procedures are in place for data access. The environment logs are audited by Information Services (IS). Any additional data collection needed will be performed in RedCap and stored in the thoracic protected drive.

The PI and research team will take all the recommended steps to protect all personal information. After the matching and database creation, the individuals will be assigned a unique code in order to de-identify the data. Only the PI and the data manager analyst assigned for the project and will have access to the code list, which contains the information necessary to re-identify the data. All data are kept confidential and accessible only to researchers on this study. The paper documents will be secured and shredded after six years of the end of the study. The electronic de-identified database will NOT be destroyed and will be maintained in a secure host at the secure drive. The coded list will be destroyed using secure deletion utility after six years after the end of the study.

28. Compensation for Research-Related Injury

NA

29. Economic Burden to Subjects

There will be no costs associated with the use of Tamsulosin under this study. The study will cover the costs of the medication given to subjects. The ultrasound used for post void residual measurement will be provided by the Thoracic Surgery Division. For all patients who agree to participate in the prospective trial, measurements will be done by a research assistant at no cost to the patient. This study was approved for a quality improvement grant under the UMass Memorial Health Care.

30. Consent Process

In order to ensure that all study staff are familiar with and will follow HRP-802 Investigator Guidance, all the team members will have a discussion joint on the components of the form. During this time, any questions or confusion will be addressed. The consent process and discussion of the research will occur during the clinic visit prior to the surgery. There will be no waiting period between recruitment and obtaining consent, since both will occur at the same time during the clinic

visit. In order to ensure ongoing consent, we will ask the patients again during the last visit prior to their surgery if they would still like to participate in the research.

To obtain informed consent from non-English speaking subjects, the informed consent will be translated in Spanish and Portuguese. If needed, any information can be clarified by using phone interpreter services.

31. PROCESS TO DOCUMENT CONSENT IN WRITING

We will be obtaining consent in writing. In order to ensure that all study staff are familiar with and will follow HRP-803 Investigator Guidance, all the team members will discuss the components of the form. During this time, any questions or confusion will be addressed. The consent will predominantly be obtained by the research assistants on the team.

During the COVID -19 pandemic, surgical discussions are being conducted virtually. It is therefore not feasible to obtain written consent from the subject in person. During their telehealth visit, potential subjects will be informed of the study and offered the option to participate. The study will be explained to them in detail and all questions will be answered. If they are interested, two consents will be sent to them either by standard mail, with a self-addressed stamped envelope to return the signed consent or electronically with the option of returning a signed copy electronically or by standard mail.

32. DRUGS OR DEVICES

Patients will take 0.4 mg tamsulosin for two evenings prior to surgery as well as the day of surgery prior to the operation. The medication will be dispensed from IDS. According to the HRP-425[15], and the FDA Guidelines[16,17], the study drug, Tamulosin fulfills the following criteria, and thus is exempt of IND.

- Determination: The drug is lawfully marketed in the United States
- Determination: The investigation does not involve a route, dosage level, or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product

- Determination: Evidence of FDA approval and FDA-approved indications is in the protocol file

The project obtained from Food Drug Administration the IND exemption ref PIND 148434

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