Title: Does Tamsulosin Decrease Postoperative Urinary Retention in Spine Surgery? A Double-Blind, Randomized Controlled Trial

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1.0 Introduction

Postoperative urinary retention (POUR) is a common complication following certain surgical operations. While much is known about the innervation and neural regulation of bladder emptying and storage, the cause of urinary retention after surgery is not fully understood. Early research has indicated that a small dose of tamsulosin (Flomax®), a commonly used medication approved to treat urinary symptoms in men with benign prostatic hypertrophy, may reduce the incidence of POUR. Urinary retention is a prevalent issue in patients undergoing spinal surgery, leading to patient discomfort and prolonged length of stay. We hypothesize that the use of perioperative tamsulosin in patients undergoing spinal surgery will decrease the incidence of POUR.

2.0 Background

In the United States, estimates of POUR rates range from 2% to 70%[1, 2]. This wide range is due to multiple factors affecting its incidence, including anesthetic regimen, duration and type of surgery, age, gender, co-morbidities and presence of pre-operative urinary symptoms[2]. There is a paucity of literature specific to spine patients, but published rates in this population range from 5% to 38%[3-5]. POUR can be painful, physically damaging, and emotionally troubling for patients.

Up to 22% of patients that develop POUR receive an intra-urethral catheter[6], which places them at an increased risk of developing hospital-acquired urinary tract infections. These catheter-associated urinary tract infections (CAUTIs) significantly contribute to patient morbidity, increase the average length of hospital stay, and are associated with increased inpatient mortality[2, 7]. CAUTIs also have a significant financial impact, costing U.S. hospitals an estimated $400 million annually[8]. This is especially significant since the Centers for Medicare and Medicaid no longer compensate hospitals for the additional cost of treating CAUTIs, believing them to be reasonably preventable[9].

The exact pathogenesis of POUR is not well understood. One theory is that over-activation of alpha-adrenergic nerve receptors on the human bladder is an important contributor to urinary retention after surgery[10]. This theory is based on current understanding of bladder physiology and the fact that many agents such as ephedrine used during general anesthesia have activity at alpha-adrenergic receptors. Patients treated with ephedrine have been shown to be at increased risk of developing urinary retention [11, 12].

Tamsulosin, a medication that blocks these alpha-adrenergic receptors, has been shown to significantly reduce the incidence of POUR in specific surgeries when given preoperatively[13-15]. This drug, which is FDA approved and widely used to treat symptoms of bladder outlet obstruction and benign prostatic hypertrophy (BPH) in males, has a favorable side effect profile and a half-life of 9-15 hours, achieving steady state after 5 days with daily dosing[16]. While previous studies have demonstrated the practicality, efficacy, and safety of prophylactic tamsulosin for POUR, the trials were small and only examined urinary retention in patients undergoing hernia repair and other general surgical procedures; no spinal surgery patients were included in these trials.

Madani and colleagues had the largest trial, randomizing 232 male patients undergoing inguinal or scrotal surgery to either tamsulosin or placebo[14]. While they found that tamsulosin dramatically reduced the incidence of POUR (5.9% with tamsulosin vs 21.1% with placebo; p = .001), the patient population differs from our spine patients. This study also excluded patients with excessive perioperative fluid intake and duration of surgery greater than 90 minutes, both of which are populations at risk for POUR and therefore should be studied. Mohammadi-Fallah and colleagues found a similar reduction in POUR in their randomized trial (2.5% with tamsulosin vs 15% with placebo; p = .04), though the numbers were very small (n=80) and the patient population underwent inguinal herniorrhapy[13]. Both of these studies administered study drug no more than 14 hours prior to surgery. The third and most recent study by Poylin and colleagues was a retrospective review in men undergoing pelvic surgery; tamsulosin was given at the discretion of the surgeon 3 days prior to surgery[15]. Their findings were in line with previous work, with a rate of POUR of 6.7% in the tamsulosin group and 25% in the control group (p = .029). In none of these studies were there complications or adverse events attributable to tamsulosin.

At Maine Medical Center (MMC), there are approximately 2600 elective spinal surgeries annually. Nearly half of these patients are males over age 50, who have an increased risk of developing POUR[3]. Over the past three years, over 1900 males aged 50 years or greater have undergone elective spinal surgery at MMC, and within this group approximately 17% have developed POUR.

Currently, the administration of preoperative prophylactic tamsulosin is standard practice at MMP Orthopedics, given to high risk male patients who are undergoing total joint replacement. A modified version of the International Prostate Symptom Score is administered preoperatively, and if the score is ≥ 6, these patients are given a course of tamsulosin (3 days preop and continuing 7 days after discharge). Although they have no formal data, providers and nursing staff believe the incidence of POUR has decreased substantially, and aside from occasional episodes of transient hypotension, there have been no safety issues with this practice.

We propose a randomized, double-blinded, placebo-controlled investigation of the impact of perioperative tamsulosin on the incidence of POUR in patients undergoing elective spine surgery.

3.0 Study Objectives

3.1 Primary Objective

This trial will test the hypothesis that prophylactic administration of tamsulosin will reduce the incidence of POUR compared to placebo, and will not increase the risk of adverse events in this setting.

3.2 Secondary Objectives

Secondary analyses will include

- Treatment difference in length of stay
- Treatment difference in time to first spontaneous void

- Relationship between preoperative post-void residual (PVR) and POUR
- Correlation of baseline IPSS and POUR
- Relationship between duration of surgery and POUR

4.0 Design

The study is a prospective, double-blind, randomized, placebo-controlled trial. Subjects will be randomized 1:1 to receive either oral tamsulosin 0.4 mg or placebo, taken once each evening, beginning 5 days prior to surgery and continuing through the first postoperative day. The primary endpoint is met when the patient is able to spontaneously empty their bladder post-operatively, or needs to be catheterized with either a straight or indwelling urinary catheter for post-operative urinary retention, whichever occurs first.

5.0 Subjects

Subjects are males age 50 to 85 undergoing elective spine surgery at Maine Medical Center who have surgery scheduled at least 5 days following enrollment, and are seen preoperatively at MMP Neurosurgery and Spine (MMP NSS).

5.1 Inclusion

- Male patients 50 to 85 years old
- Undergoing elective spine surgery at least 5 days after enrollment
- Preop visit done at MMP Neurosurgery and Spine
- Surgery to be done at Maine Medical Center

5.2 Exclusion

- Currently on tamsulosin or other alpha-adrenergic blocking drug
- Allergy to tamsulosin
- Allergy to lactose
- Serious or life-threatening allergy to sulfa drugs
- Emergent procedure
- Patients with spinal trauma, spinal infection or spinal cord tumor
- Patients with pre-existing indwelling urinary catheter
- Patients with a diagnosis of orthostatic hypotension, or orthostatic hypotension as defined by one or more of the following:
  - decrease in systolic blood pressure ≥20 mm from sitting to standing
  - decrease in diastolic blood pressure ≥10 mm from sitting to standing,
  - clinical symptoms of orthostatic hypotension upon standing (faintness, lightheadedness, vertigo)
- History of prior urethral or bladder surgery
- History of prostatectomy or other prostate surgery
- Patients with renal failure
- Non-English speaking
- Scheduled for cataract surgery within two weeks of study drug dosing

- Unable to provide informed consent (e.g. severe dementia)

6.0 Procedures

6.1 Screening and Consent

Eligible male patients will be screened and offered the opportunity for voluntary participation in this study at the preoperative office visit or initial consultation. The research consent form will be reviewed with the patient, who will have up to 5 days before surgery to decide on participation. Patients can provide informed consent during the office visit or can choose to return to the office at least 5 days prior to surgery for consent and randomization. Consenting may be done by CITI-trained attending surgeon, PA, staff nurse or research nurse. Consenting process will be documented in patient chart, and copy of informed consent will be given to patient and also scanned into chart.

6.2 Outpatient procedures

After patient consent is obtained, all study patients will undergo a non-invasive post-void bladder scan via portable ultrasound to measure PVR. In addition, study staff will obtain a modified International Prostate Symptom Score (IPSS), a short survey to measure baseline lower urinary tract symptoms[17].

At this time, patients will also have orthostatic blood pressure measurements taken as follows:

- BP and pulse taken while patient is laying down and sitting
- BP and pulse taken after patient goes from sitting to standing

If patient meets definition of having orthostatic hypotension as described in 5.2 Exclusion Criteria, he will be excluded from study participation. A record of all patients screened and excluded for this reason will be kept with study documents. After PVR, BP and IPSS, patient will be given prescription for 7 days of study drug. Patient will be instructed to begin once daily evening administration of study drug five days prior to surgery, and to continue self-medication up to and including the night before surgery. Patients will record study drug administration on a drug diary card, given by office staff. Patient will be instructed to keep two doses at home for possible dosing after surgery, depending on discharge date. Patient and office providers will be blinded to the assigned medication.

Computer-generated 1:1 randomization (without blocking) will be done by the MMC pharmacy, which will place a seven day supply of tamsulosin 0.4 mg or placebo in sequentially numbered envelopes corresponding to study ID prior to study start. Study drug will be kept in and dispensed from locked cabinet in research coordinator's office. Study staff will access locked cabinet and pull next available envelope to give to consented patient. Study ID number will be logged into study binder kept in locked cabinet.

6.3 Inpatient procedures

On hospital admission, MMC pharmacy will be informed of patient's inclusion in DRIPS study, and will be directed to dispense appropriate study drug (based on study ID number) on first postoperative night and on postoperative day one. All members of care team will be blinded to study drug assignment.

Patients discharged before evening of postoperative day one will be instructed to take study drug as described in section 6.6 below, with instructions given to both patient and family member if present.

In cases of potential urinary retention, inpatient portable bladder scans will be performed by unit nurses, who have been trained in this procedure.

6.4 Bladder Scans

Outpatient bladder scans done at MMP NSS will be done with a portable bladder scanner (SRS Medical Uroscan), used only for study purposes. This totally non-invasive test uses ultrasound technology to create a three-dimensional image of the bladder and calculate volume based on this image. Immediately after patient voids, he will be instructed to lay in supine position. Ultrasound gel will be applied to external probe, which will be placed on abdomen and urine volume will be displayed on device.

Because bladder scan by ultrasound is not a standard practice at MMP NSS, a study staff of at least five office-based nurses and/or medical assistants (MAs) will be trained in the proper use of the bladder ultrasound device. Training will be done by a representative of the bladder scanner manufacturer, or a nurse educator from an inpatient unit with a high volume of bladder scans (e.g. PACU); a log of trained MMP NSS nurses and MAs will be maintained in the regulatory binder. A daily "on-call" schedule of the bladder scan team will be developed and accessible to study staff via an Outlook calendar. Once a patient has given informed consent, the on-call team member of the day will be contacted to perform the scan and record the results in the patients' study chart.

Bladder scans done on inpatients at MMC will be standard of care and will be done by nurses who are already trained in the procedure. Technique is identical to that described above. Various makes and models are in use at MMC, but all are portable, with similar mechanisms of action. This procedure is familiar to all floor nurses at MMC, so no additional training will be necessary.

6.5 Postoperative considerations

Post-operative care of study patients will include orders for the MMC Acute Retention Protocol, as follows:

- If patient has not voided after 4 to 6 hours or is uncomfortable, a bladder scan is done.
- Straight catheterization is done if bladder scan volumes are greater than 300 to 500 cc (defer if patient is known to chronically retain high volumes and is not uncomfortable).

All patients with POUR will be treated as deemed necessary by the medical team. Treatment of any patient that has POUR will not be guided or constrained by this study.

6.6 Follow-up

Patients discharged before full course of study drug is given (two postoperative doses) will be instructed to take study drug at home as outlined on patient instruction card, specifically: Patients discharged on day of surgery will take two doses at home (on day 0 and day 1 postop); patients discharged on day 1 postop will take one dose at home; and patients discharged after day 1 postop will not take any study drug. Patients will be advised to discard remaining study drug.

As part of standard of care, it is routine for nursing staff at MMP NSS to follow up with patients via phone call within 24 hours of discharge. As a part of this call, all study patients will be queried on any issues related to urinary retention. They will also be asked if they have continued their study medication as instructed.

7.0 Blinding

This is a double-blind study (i.e. the patient and investigators are both unaware of the specific study drug being administered).

Measures will be taken by the MMC Pharmacy to ensure tamsulosin and placebo are indistinguishable with regards to capsule shape, color and size. This will be done by inserting the tamsulosin capsule into a size 0 blue and white gelatin capsule (overlay), and formulating an identical capsule filled with lactose for the placebo.

In the event of a serious adverse event, the blind may be broken by contacting the study coordinator or principal investigator, who would in turn contact the pharmacy to determine whether the patient was on tamsulosin or placebo.

8.0 Outcome

8.1 Primary Outcome

The primary outcome measure will be post-operative urinary retention, defined as the need for post-operative urinary catheterization for acute retention as defined by the MMC Acute Retention Protocol, or re-catheterization in those patients who leave the operating room with an indwelling catheter.

8.2 Secondary Outcome

Secondary outcome measures to be examined are length of stay, relationship between pre-operative PVR and POUR, correlation of baseline IPSS and POUR, relationship of surgical time to POUR, and time to first spontaneous void.

9.0 Potential Risks

The study drug, tamsulosin, is generally considered safe with few side effects. The risk of improper disclosure of private medical information is possible, but is no greater than that inherent in the everyday practice of medicine. Potential risks will be disclosed as part of the informed consent process.

9.1 Side Effects of tamsulosin

Specific side effects of tamsulosin and their reported frequency are[16] :
Greater than 10%:

- Orthostatic hypotension (first dose: 6% to 19%; symptomatic orthostatic hypotension (chronic therapy) <1%)
- Headache (19% to 21%), dizziness (15% to 17%)
- Ejaculation failure (8% to 18%)
- Infection (9% to 11%)
  Rhinitis (13% to 18%)
  1% to 10%:
- Drowsiness (3% to 4%), insomnia (1% to 2%), vertigo (≤1%)
- Loss of libido (2%)
- Diarrhea (6%), nausea (4%)
- Weakness (8% to 9%), back pain (7% to 8%)
- Blurred vision (≤2%)
- Pharyngitis (6%), cough (3% to 5%), sinusitis (4%)
  Less than 1% (Limited to important or life-threatening):
- Epistaxis, exfoliative dermatitis, hypersensitivity reaction, hypotension, intraoperative floppy iris syndrome (IFIS), palpitations, priapism, syncope

With the exception of IFIS, all of these potential side effects are reversible. These and all other adverse effects, expected and unexpected, will be documented and reported.

9.2 Serious Adverse Events

Any event occurring while a patient is on study that meets the following criteria will be considered a Serious Adverse Event:

- Death
- Life-threatening (i.e. immediate risk of death)
- Readmission or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

Important adverse events that may not result in death, may not be life –threatening, or do not require hospitalization may be considered serious when they may acutely jeopardize the patient without immediate medical attention to prevent one of the

outcomes listed above. Serious may also include any other event deemed as such by the investigator.

All serious adverse events will be monitored by clinical and/or research staff. The relationship of the adverse event to the study drug will be categorized as Not related, Unlikely to be related, Possibly related, Probably related and Definitely related. All serious adverse events will be reported to the IRB and DSMB within 5 days.

In the case of a serious drug-related adverse event, study drug will be discontinued and patients will continue to be followed.

9.3 Confidentiality

Each study subject will be assigned a unique study ID number, which will be linked to their identifying information by a key. This linking key will be kept separate from the data collection forms, locked and secure in the study coordinator's office. Study findings will be summarized and presented in a manner in which individuals will not be identifiable.

9.4 Data Safety Monitoring Board

This study will use a Data Safety Monitoring Board (DSMB). Details of the DSMB for this study are contained in the attached DSMB Plan.

10.0 Analytic Methods

10.1 Data collection

Data will be collected prospectively by study staff in the office, at the bedside and through Epic chart review. A study ID will be assigned to each patient and study documents will all use this ID to collect data. Identifiable data will be stored separately. Baseline variables to be collected will include basic demographics, past medical history and medication list, PVR and IPSS. Operative data will include type and duration of surgery, fluid intake, medications given, and any perioperative urinary catheterization. Data will be recorded postoperatively will include fluid balance, need for urinary catheterization, pain medication and adverse events.

All data will be recorded on a data collection sheet (see attached data sheet). PVR and IPSS done in the MMP NSS office will also be recorded on separate forms (see attached PVR and IPSS forms), which will be linked to the primary data collection sheet. These data sheets will be stored in a locked and secure area of the study coordinator's office.

RedCap, a HIPAA-compliant database, will be used to store all information after it is collected. Data entry and access will only be allowed to research coordinator and Principal Investigator.

10.2 Sample Size and Power Calculations

Tamsulosin is hypothesized to reduce POUR compared to placebo in males. Observational data from our center shows a POUR rate of about 17% in patients similar to those to be included in the trial. We hypothesize that the use of the drug can reduce this rate by 50%. A two group continuity corrected c^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between a control group proportion of 0.170 and a treatment group proportion of 0.085 (odds ratio of 0.454) when the sample size in each group is 264 and a total sample size of 528.

We anticipate recruiting 264 evaluable patients in each group who took at least one dose of study drug and who also had surgery. Due to expected patient drop-out (from surgery cancellations, patients changing their mind or forgetting to take study drug), we expect to enroll up to 610 patients to achieve this.

In a recent chart review, it was found that 670 potentially eligible male patients (age 50-85 and not on preoperative tamsulosin) were seen at MMP NSS in FY 2014, and 680 were seen in FY 2015. Given this volume of patients undergoing spine surgery at MMC, it seems reasonable to expect we could accrue our target enrollment in three years.

10.3 Randomization

To evaluate the success of randomization, characteristics of patients in the treatment and control groups will be compared using t-tests or their non-parametric equivalents, as appropriate, for continuous variables and chi-square tests or Fisher's exact tests, as appropriate, for categorical variables. The primary outcome, incidence of POUR, will be compared across groups using chi-square tests. If large baseline imbalances between groups are found, a secondary analysis will be performed using a logistic regression model, with POUR as the outcome variable, treatment group as the predictor of interest, and imbalanced patient characteristics as confounding variables. Secondary objectives examine the relationship between other factors and POUR and will be analyzed similarly. Length of stay and time to first void will be analyzed as continuous variables, using t-tests and linear regression models.

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