The use of an uroselective Alpha-1-antagonist to reduce the incidence and duration of postoperative urinary retention following spine surgery

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Title:

The Use of a Uroselective Alpha-1-Adrenergic Receptor Antagonist to Reduce the Incidence of Postoperative Urinary Retention Following Spine Surgery

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Abstract:

Postoperative urinary retention (POUR) occurs in up to 38% of neurosurgical patients undergoing simple decompressive spine procedures, with even higher rates estimated after complex spinal procedures such as instrumented fusion. This can result in multiple intermittent catheterizations for bladder decompression, increased incidences of urinary tract infection, and prolonged hospital stays. Previous non-neurosurgical series using nonspecific alpha-1-adrenergic receptor antagonists have had some success in both the prevention and treatment of POUR. However, according to a recent Cochrane review, the use of alpha-blockers for the prevention and treatment of POUR is under-researched and there remains a need for well-designed clinical trials evaluating these drugs. The current neurosurgical practice at Mayo Clinic has both the clinical volume and infrastructure to support a randomized controlled trial evaluating the use of tamsulosin, a uroselective alpha-1-adrenergic receptor antagonist, for the prevention and treatment of POUR. If successful, this could not only result in decreased incidence and duration of POUR, but also in decreased hospital stays with an associated significant reduction in healthcare costs.

Background:

Postoperative urinary retention (POUR) is a common problem following neurosurgical procedures, specifically spine surgery. Estimates of incidence of POUR range from 2 to 69% in various surgical series depending on the type of surgery, anesthetic technique, and the method used to evaluate urinary retention.[1-8] In the only neurosurgical series specifically addressing the incidence of POUR, it was found to occur in 38% of patients undergoing simple decompressive spine surgeries with nearly an equal distribution between men

(39.1%) and women (36.2%).[9] The current mainstay of treatment for POUR is intermittent catheterization for bladder decompression until the retention resolves and the patient can void spontaneously. This can result in increased rates of bacteremia and urinary tract infection (UTI).[10,11] Furthermore, POUR has been shown to prolong hospital stay.[9]

While many factors likely lead to the development of POUR, increased sympathetic outflow is thought to be central to its pathogenesis.[12-14] The bladder and urethra are innervated by both the parasympathetic and sympathetic nervous systems. While cholinergic receptors and beta-receptors are concentrated in the body of the bladder, alpha-adrenergic receptors are primarily localized in the bladder neck, proximal urethra, and prostate gland, with a relative high density of the 1A subtype.[13,15-17] Stimulation of alpha-adrenergic receptors leads to smooth muscle contraction and increased tone. Increased sympathetic discharge can lead to overactivation of these alpha-1-adrenergic receptors resulting in increased closing pressure and outflow resistance at the level of the bladder neck and proximal urethra, which can cause POUR.[12,13] In the surgical patient there are a number of reasons for increased sympathetic discharge that can lead to POUR. First, bladder distention alone can cause an increase in sympathetic motor activity,[18] which is common in surgical patients who are given intravenous fluids perioperatively. Second, there is an increase in sympathetic outflow as the body's systemic response to the stress of surgery. Finally, postoperative pain results in increased sympathetic firing.

Multiple other risk factors have been associated with increased rates of urinary retention in the postoperative period. These include increasing age,[1-4,9,19,20] longer duration of surgery,[1,3,4,19-22] anesthetic technique,[1,7,23] total intravenous fluid administered perioperatively,[4,6,19] diabetes mellitus,[3] post-operative analgesia,[3,6,24] and previous history of voiding dysfunction.[25] Unfortunately, many of these risk factors cannot be directly modified in the individual patient, such as age, operative time, the use of general anesthesia, or limiting intravenous fluid administration without potentially putting patients at risk.

Two main intervention strategies have been investigated to overcome urinary retention by facilitating bladder emptying. The first is to augment contraction of the detrusor muscle by stimulation of postsynaptic parasympathetic receptors in the wall of the bladder using anticholinesterases. This strategy has been met with limited success in most studies and has been largely abandoned.[13,26-28] Bedside uroflowmetry studies in patients experiencing retention have shown that POUR occurs despite active contraction of the detrusor muscle, implicating outlet obstruction as the more important mechanism.[29] This has led to the second strategy, which is to relieve obstruction at the bladder outlet and thereby facilitate bladder emptying. As discussed above, increased sympathetic outflow during the perioperative and postoperative period can result in increased muscle tone at the bladder outlet due to activation of alpha-1-adrenergic receptors. Thus, blockade of these alpha-1-adrenergic receptors should result in relaxation of

these structures and augment bladder emptying, thereby reducing both the incidence and duration of POUR.

Previous studies have shown benefit in using nonspecific alpha-1-adrenergic receptor antagonists (phenoxybenzamine, alfuzosin, and prazosin) in the perioperative period to reduce the incidence and duration of urinary retention postoperatively. Several non-neurosurgical series, have demonstrated reduced incidence of POUR, fewer required catheterizations, and a decrease in UTIs in patients treated with alpha-1-adrenergic receptor blockade.[12,13,30-36] Two studies did not show a benefit of alpha-adrenergic receptor blockade for POUR. The first study randomized hemorrhoidectomy patients into treatment groups consisting of prazosin and placebo.[37] No difference was found in the incidence of urinary retention. However, a large limitation of this study was that all patients underwent spinal anesthesia, an important independent risk factor for urinary retention that may have prolonged effects on the ability of the detrusor muscle to contract due to blockade of the parasympathetic innervation to the muscle.[1,38] Additionally, only 46 total patients were randomized raising questions of adequate sample size. The second negative study compared the use of alfuzosin to a combination of carbachol/diazepam and placebo.[39] In this study, subjects were not pretreated with alfuzosin and were given the medications only after having an inability to void six hours or more after surgery. This may have resulted in over-distention of the bladder and detrusor atony, which is a known complication of excess intravenous fluid administration resulting in retention.[40] Furthermore, there may have been inadequate time for the drug to reach therapeutic steady state concentrations and thus underestimated the potential benefit of the medication.

Despite some success with nonspecific alpha-1-adrenergic receptor antagonists in the prevention and treatment of POUR, it remains a common surgical complication and perioperative alpha blockade has not yet become the standard of care for high-risk patients or procedures. In a recent Cochrane review analyzing drug treatment for POUR, the following statement was made: “The potential of drugs in treating post-operative urinary retention should be further investigated, including alpha blockers, which appear to have been under-researched considering their theoretical usefulness. There remains a need for well-designed and adequately powered trials to assess the effectiveness of drugs for the treatment of post-operative urinary retention, a common surgical complication.”[41] To date, no studies have been reported using newer uroselective alpha-1-adrenergic receptor antagonists, such as tamsulosin, in postoperative patients. Based on prior reports of success with nonspecific alpha-1-antagonists, it is hypothesized that treatment with tamsulosin will result in even greater benefit towards reducing urinary retention with fewer side effects due to its uroselective nature. Prior studies have shown reduced incidences of dizziness, hypotension, and dry mouth with tamsulosin when compared to nonspecific alpha-adrenergic receptor antagonists.[42]

Tamsulosin has been approved for use in treating the signs and symptoms of benign prostatic hyperplasia in males. Its mechanism of action is through blockade of alpha-1-adrenoreceptors at the bladder neck and prostatic urethra resulting in improvement of bladder outlet obstruction and reduction of maximum voiding detrusor pressure. As opposed to nonspecific alpha-1-adregnergic antagonists, tamsulosin has a higher affinity for the alpha-1A adrenergic receptor subtype, which comprises the majority of alpha-receptors in the lower urinary tract, compared to the alpha-1B subtype primarily located in vascular smooth muscle. It is metabolized in the liver and excreted primarily through the kidney. Dosing adjustments are recommended only in patients with severe liver disease or end-stage renal failure. Time to maximum concentration is 4-8 hours after administration in the fasting state, and patients reach steady state concentrations after approximately 5 days of therapy. Significant adverse events have been reported rarely. These include signs and symptoms of orthostasis (0.2%), priapism (rare, <1 in 50,000), and intraoperative floppy iris syndrome (rare reports during cataract surgery).[16] While currently only FDA approved for use in males, studies have also demonstrated efficacy in treating urinary retention and voiding difficulty in females as well.[43-45]

Rationale:

Decompressive laminectomy and spinal fusion procedures are among the most common neurosurgical procedures performed. POUR is a frequent complication of such surgeries and impacts a large proportion of this population resulting in multiple intermittent bladder catheterizations for bladder decompression, increased incidence of bacteremia, increased incidence of UTIs, and prolonged hospital stays. Use of a uroselective alpha-1-adrenergic receptor antagonist, such as tamsulosin, in the perioperative period (medication started five days prior to surgery and taken until hospital discharge) could reduce both the incidence and duration of postoperative urinary retention, resulting in shorter hospital stays and decreased healthcare costs.

Hypothesis 1: Tamsulosin started five days preoperatively and taken until hospital discharge will significantly decrease the **incidence** of postoperative urinary retention among neurosurgical patients undergoing decompressive laminectomy and/or spinal fusion procedures compared to placebo. (Primary Hypothesis)

Hypothesis 2: Tamsulosin started five days preoperatively and taken until hospital discharge will significantly decrease the **duration** of postoperative urinary retention among neurosurgical patients undergoing decompressive laminectomy and/or spinal fusion procedures who experience this surgical complication compared to placebo. (Secondary Hypothesis)

Hypothesis 3: Tamsulosin started five days preoperatively and taken until hospital discharge will significantly decrease the length of hospital stay among neurosurgical patients undergoing decompressive laminectomy and/or spinal fusion procedures compared to placebo. (Secondary Hypothesis)

Specific Aims:

1) To determine if the use of a uroselective alpha-1-adrenergic receptor antagonist during the perioperative period reduces the incidence and duration of POUR in neurosurgical patients undergoing decompressive laminectomy and/or spinal fusion.
2) To determine if reduced incidence and duration of POUR in this patient population will result in decreased length of hospital stay.

Experimental Design:

The study design will be a prospective randomized controlled double-blinded clinical trial comparing a uroselective alpha-1-adrenergic receptor antagonist (tamsulosin, 0.4mg per day) with placebo in neurosurgical patients undergoing decompressive cervical or lumbar laminectomy and/or spinal fusion. The study population will consist of all neurosurgical patients undergoing decompressive laminectomy and/or spinal fusion at Mayo Clinic Rochester from the time of study initiation (early 2012) that meet inclusionary criteria, do not meet any exclusionary criteria, and give consent to enter the study. Patients that enter the study will be randomized to receive tamsulosin (treatment group) or placebo (control group). The primary outcome variable will be the incidence of POUR. Secondary outcome variables of interest will include duration of POUR and length of hospital stay. Additional variables (demographic factors, number of catheterizations, incidence of UTI, etc.) will also be collected for comparison of the homogeneity of the two groups with respect to known confounding factors and to analyze other outcomes of interest. Data on all outcome variables will be collected by the time of hospital discharge. Therefore, this study will require minimum follow up time and it is estimated that patients will actively be participating in the study for an average of 8-12 days. Patients and providers will be blinded to treatment assignment for the duration of the study.

Based on sample size calculations (see Analysis of the Data section below), it is estimated that 175 patients will need to be recruited into each group. The Department of Neurological Surgery at Mayo Clinic Rochester performs approximately 4000 major neurosurgical procedures per year, of which approximately half are spinal procedures. Of those, approximately 1000 cases should meet the surgical criteria for this study. Thus, it is estimated that a one-year time frame will provide sufficient time to recruit the necessary 350 patients and perform the study.

Methods:

Subject Recruitment and Retention:

Study subjects will be recruited through referral for surgical consultation in the neurosurgery outpatient clinic at Mayo Clinic Rochester. Individual surgeons will determine whether a surgery is indicated in particular patients. After the decision has been made to proceed with surgery, the patient will be interviewed for eligibility into the study, consented, and enrolled by the respective neurosurgeon's physician extender (R.N. or N.P.). Eligibility criteria are included in Table 1 and will be reviewed with each patient during the preoperative visit addressing the eligibility requirements for entry into the study. Patients undergoing simple spinal procedures (discectomy and foraminotomy procedures) that typically have next day hospital discharges and low incidences of POUR will be excluded from the study. It is not anticipated that subject retention will present a major challenge because the duration of study follow up is limited to the duration of the postoperative hospital stay. It is estimated that subjects will be actively participating in the study for approximately 8-12 days in most cases. Subject recruitment will continue until at least 175 subjects have been recruited into both the treatment and control groups and have completed the study. An interim analysis will be performed with unblinded data from the research pharmacy when 75 or more patients have completed participation.

Table 1:

Inclusion Criteria	Exclusion Criteria
≥ 35 years (Males & Females)	< 35 years
Cervical Laminectomy Cervical Posterior Fusion Cervical Anterior/Posterior Fusion Lumbar Laminectomy Lumbar Posterolateral Fusion Lumbar Interbody Fusion	Cervical Anterior Discectomy and Fusion Cervical Anterior Corpectomy Cervical Posterior Discectomy Cervical Foraminotomy Lumbar Discectomy (METRx or Open) Lumbar Foraminotomy Lumbar Anterior Fusion
	Myelopathy with bladder dysfunction
	Patients currently taking an alpha-antagonist[#]
	Patients with history of allergy or sensitivity to tamsulosin or other alpha-antagonist
	History of prostatectomy or urologic surgery involving the bladder or urethra
	Severe liver disease or end-stage renal disease

	Patients taking strong inhibitors of CYP3A4*
	Mental disability or prisoner

#The following drugs are alpha antagonists: alfuzosin, doxazosin, prazosin, terazosin, tamsulosin, and phenoxybenzamine.[46,47]

*The following drugs are strong inhibitors of CYP3A4: ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir/ritonavir, lopinavir/ritonavir, and conivaptan.[48]

Randomization:

A consecutive sample of subjects that meet eligibility requirements and give informed consent will be randomized to two study groups via a randomization number generated from a random numbers table. Based on their randomization number patients will be given a prescription (for either tamsulosin or a like-appearing placebo) from the Mayo pharmacy at least one week prior to the date of surgery. The pharmacy will record which group the patient has been assigned to in a central pharmacy database. This database will then be used in the perioperative and postoperative period to maintain the patient's drug designation and administration while in the hospital. The randomization will be blinded to both the treating physician's team and the patient until the end of the study and data analysis is undertaken.

Drug Administration:

In order to achieve full steady state concentrations of the drug by the time of surgery, patients will be instructed to take the assigned drug for 5 days prior to surgery, as well as the morning of surgery. Thus, patients will be given 6 pills of the study medication or the like-appearing placebo at a preoperative clinic visit. On the morning of surgery patients will be admitted to Saint Marys Hospital as morning admissions and proceed to surgery that day based on the surgical schedule. Data on medication compliance will be collected and recorded at that time. Patients will continue taking tamsulosin 0.4mg or like-appearing placebo provided by the Mayo Pharmacy beginning on post-operative day one and continuing every day during their postoperative hospital course until the time of discharge. At that time the primary treating team will write an order to discontinue the study medication. Because each patient will be at therapeutic steady state concentrations of the drug by the time of surgery, shorter hospital stays should not underestimate the potential treatment benefit of this medication. Standard postoperative orders for patients undergoing decompressive cervical or lumbar laminectomy and/or spinal fusion have been in place for neurosurgical patients and will continue to be used during this study (postoperative order set

MC1156-404). The cost of the study medication will be covered by the study and patients will not be charged.

Pre-operative Post Void Residual Urine Volume:

A pre-operative post void residual (PVR) volume of urine will be obtained on all enrolled patients at their pre-operative clinic visit prior to beginning their drug assignment (tamsulosin or placebo). This will be measured using the same technique as will be performed during the post-operative period (see Outcome Measures below). This baseline PVR will help determine efficacy of the study drug as outcomes are measured. The residual will be done by a member of the study staff and patients will not be charged.

Outcome Measures:

The primary outcome measure will be the incidence of POUR. POUR will be defined as any of the following:

1) Estimated post-void residual (PVR) volume of urine greater than or equal to 300 mL.
2) Estimated retention urine volume of greater than or equal to 500 mL in patients unable to void.
3) Patients experiencing discomfort or distension and unable to void with lesser residual urine volume than 500 ml

Neurosurgical nursing staff currently follow the institutional Urinary Retention Protocol (MC1156-214rev0610.) This protocol includes an algorithm for both diagnosing postoperative urinary retention and its treatment. This protocol has been in use for all postoperative spine patients since 2003 and the most current version is based on the above definition of urinary retention. All residual volume of urine measurements will be made with a standard bladder scanner instrument that is currently in use on the neurosurgery wards. Presence or absence of urinary retention will be recorded in the electronic medical record (EMR) for later data retrieval and analysis.

Secondary outcome variables include duration of POUR among those patients in which it occurs, number of intermittent catheterizations in those with urinary retention, incidence of UTI, and duration of hospital stay. Measurement of the duration of POUR will closely coincide with the methods for recording incidence of POUR as discussed above. The decision to use and the time of removal of indwelling urinary catheters will be left to the discretion of the primary neurosurgical team. Time of indwelling catheter removal after surgery will serve as time zero for beginning calculation of postoperative urinary retention duration if the patient later requires in and out straight catheterization. For patients without an indwelling catheter, the time patients leave the operating room will serve as time zero. Per the Urinary Retention Protocol (MC1156-214rev0610),

patients found to be experiencing POUR will be ordered to have a straight in and out catheterization performed by a member of the catheterization team after failure of noninvasive measures (e.g. trigger techniques, bladder massage, application of warmth, relaxed environment, privacy, ambulation) by the attending nursing staff member. Urinary retention will be considered resolved after two consecutive post-void residual urine scans have demonstrated less than 300 ml residual urine volume in a patient spontaneously voiding. The number of intermittent catheterizations is recorded in the EMR in accordance with the standardized protocol.

Patients suspicious of having a UTI based on signs and symptoms of urinary frequency, urgency, burning or pain will have a urine sample (via catheterization or spontaneous void) sent for routine urinalysis, gram stain, and culture/sensitivity by the nursing staff member responsible for the patient or the primary neurosurgical team, per instructions documented on the Urinary Retention Protocol (MC1156-214rev0610). Positive UTIs will be defined as positive gram stain in the presence of signs or symptoms of UTI, urine white blood cell count elevation, and positive culture of $>10^4$ cfu/ml. Patients will be treated with the appropriate antibiotic based on culture sensitivity.

Length of hospital stay will be recorded for all patients following the surgical procedure with the day after surgery defined as postoperative day one. The medical record will be reviewed following discharge to determine if hospital discharge date was dependent on POUR or other reason (e.g. uncontrollable pain, mobility requiring physical therapy or inpatient rehabilitation, or other medical complications delaying discharge).

In addition to the primary and secondary outcome measures, baseline characteristics will be collected on all patients via the medical record including age, height and weight, past history of postoperative urinary retention or diagnosis of benign prostatic hyperplasia (not on treatment), length and type of surgery, estimated blood loss during surgery, total intravenous fluids administered perioperatively, time to oral analgesic use (in hours), total analgesic use during the postoperative period, time to first postoperative mobility (in hours), and any adverse events thought to be related to administration of the study medication. These variables will be used as baseline comparisons between the two groups to ensure homogeny and be used in statistical adjustment if differences between the groups are significant after randomization.

<u>Unanticipated events</u>:

There is the potential for patients to experience urinary retention as outpatients after inpatient urinary retention has resolved. This is quite unusual to occur after urinary retention has resolved as defined above and may indicate the patient needs further investigation by a urologic surgeon. Patients will be counseled by nursing staff prior to dismissal regarding the signs and symptoms of urinary

retention and directed to seek medical attention with appropriate urology referral should the treating physician deem this is appropriate.

Patients experiencing prolonged postoperative urinary retention (> 5 days) will be seen by the urology consult service for recommendations regarding further investigation and treatment. The study group designation may be broken at this point to determine which group the patient is in regarding treatment medication if deemed necessary by the urology consult service to guide further treatment.

Patients experiencing severe adverse events such as profound hypotension, arrhythmia, or allergic reaction will be evaluated by the primary neurosurgical team with appropriate intervention or consultation as deemed necessary.

Quality Control:

An operations manual will be prepared prior to initiation of the study and will be distributed as necessary to all staff involved. Treating neurosurgeons and their respective physician extenders will be instructed on the study goals, risks, and expected outcomes, as well as the identification and recruitment of eligible patients to the study, including obtaining consent. Residents and staff neurosurgeons responsible for inpatients following surgery will be informed of the study goals and methodology with special emphasis on reporting adverse events and the appropriate means to resolution in conjunction with the principal investigator (PI)/co-principal investigator (Co-PI) and co-investigators prior to the study starting. Any questions or concerns arising in relation to the study will be forwarded to the primary investigator as these concerns arise.

Nursing staff responsible for patients in the postoperative period will continue to use the standard postoperative order sets for surgical patients undergoing spine procedures as well as the urinary retention protocol. An informational meeting will be arranged with the head nurses of the neurosurgical wards where postoperative patients will reside following surgery to discuss the goals, rationale, and methods particular to the study. Contact information for reporting adverse events or questions regarding study implementation will be provided before the study begins.

Any and all questions will be forwarded to the PI/Co-PI, or study co-investigators should the PI/Co-PI be unavailable, in a timely manner with multiple sources of contact available (i.e. pager, telephone numbers, e-mail addresses).

The Mayo Clinic Pharmacy will provide both the study drug (tamsulosin) and a like-appearing placebo. A labeling system to track patient assignments, but that blinds study subjects and investigators, will be utilized.

Data will be collected prospectively in an ongoing fashion for the duration of the study by investigators blinded to patient treatment group. Because the vast

majority of data will be collected from the EMR in a prospective fashion while the patient is either in the hospital or shortly thereafter, it is not anticipated that there will be much missing data.

All statistical analysis and report of results will be done in a confidential manner and no information linking individual patients with data from the study will be shared outside of the study. Every effort will be made to keep this data anonymous once it has been collected.

Analysis of the Data:

Baseline characteristics will be compared between the two study groups using a chi-squared or Fisher's Exact Test for categorical variables and multiple two sample t-tests for continuous variables. The primary outcome variable, incidence of POUR, as well as other categorical variables, such as incidence of UTI, will be analyzed using a chi-squared test or Fisher's Exact Test. Duration of POUR will be compared using a two sample non-paired t-test comparing means. An appropriate nonparametric test (e.g. Wilcoxon Rank Sum) will be used for non-normal appearing data as can be anticipated for length of hospital stay. Differences in the groups with respect to baseline variables will be used to construct a multiple linear regression model to control for potential confounding factors if necessary. Intention to treat analysis will be used for all comparisons between groups.

The primary outcome measure of incidence of POUR was used to calculate sample size. Data gathered from multiple series suggests that postoperative urinary retention occurs in 2-69% of patients undergoing a variety of surgical procedures, with 38% occurring in neurosurgical patients undergoing simple decompressive spinal procedures. Using 20% (P2=0.20) as a conservative estimate of incidence, an effect size of 10% for the primary outcome variable (P1=0.10) would be clinically meaningful. Thus, P2-P1 = 0.10. Because incidence of urinary retention is a binary categorical variable, a chi-squared test can be used to compare groups. Based on a type I error rate of 0.05 (α), a type II error rate of 0.20 (β), and power of 0.80 the estimated sample sizes needed for each group are as follows. For a one sided type 1 error, there would need to be 175 subjects in each group. For a two-sided type 1 error there would need to be 219 subjects in each group. A one-sided test of significance is reasonable in this study because an increase in incidence of POUR experienced in the tamsulosin treated group is not anticipated and would not add additional useful information in terms of using tamsulosin for POUR. Thus, a reasonable estimate for sample size is 175 subjects in both the treatment and control groups. Furthermore, with 175 patients per arm, there would be 87% power to detect a 1 day difference in the duration of urinary retention and duration of hospital stay with a 1-sided significance level of 0.05 (this assumes an effect size for this secondary outcome variable of 0.30 [1 day difference in means/pooled standard deviation estimate of 3.33]).

Role in Project:

Terry K. Schiefer: Co-Principalinvestigator for the study, responsible for study design, study implementation, data collection, reporting of adverse events, and manuscript preparation.

Jeffrey T. Jacob: Co-investigator responsible for assisting in study implementation, data collection, and manuscript preparation.

Steve Thalacker: Co-investigator responsible for IRB application, Informed Consent form, and pharmacy liaison.

Nathan Foster: Statistician responsible for overseeing statistics performed by the co-PI as part of the CTSA BERD program.

Shankar Srinivason: Member of the Office of Research and Regulatory support who will be assisting with the Investigational New Drug application and corresponding with the FDA.

Frederic B. Meyer: Co-investigator responsible for assisting with study design, study implementation, and manuscript preparation

William E. Krauss: Co-investigator responsible for assisting with study design, study implementation, and manuscript preparation

Michelle J. Clarke: Principal Investigator responsible for mentoring the primary investigator, serving as the liaison between the FDA for the Investigational New Drug application, assisting with study design, study implementation, and manuscript preparation

Mark A. Pichelmann: Co-Principal Investigator responsible for mentoring the primary investigator, assisting with study design, study implementation, and manuscript preparation.

Significance:

POUR is a common problem following spine surgery in otherwise healthy patients. It results in multiple intermittent catheterizations for bladder decompression, increased incidences of bacteremia and UTIs, and prolonged hospital stay. This study will provide insight into the effectiveness of alpha-1-adrenoreceptor blockade at the bladder neck to reduce the incidence and duration of POUR in patients undergoing neurosurgical spine procedures. If

effective, this treatment has the potential to change practice patterns in both neurosurgery and orthopedic spine practices throughout not only the United States, but also throughout the world. Perioperative use of tamsulosin, or another uroselective alpha-1-adrenoreceptor blocker, could become the standard of care. This could be especially important in the current economic environment where healthcare costs are closely scrutinized, as a reduction in both the incidence and duration of POUR could lead to shorter hospital stays and a significant decrease in healthcare spending. Furthermore, the results of this study could potentially be applied to other types of surgeries with high rates of POUR and may be the platform for starting many other clinical trials.

Human Studies Aspects:

Tamsulosin is currently only FDA approved for use in the treatment of BPH in men. With the help of the Office of Research and Regulatory Support (ORSS), an Investigational New Drug (IND) application was sent to the Food & Drug Administration (FDA) in December 2011 to use tamsulosin in this study in both men and women and was approved.

Adverse Events:

Studies using nonspecific alpha-1-adrenergic receptor blockade have shown benefit in reducing POUR with minimal adverse effects.[12,13,30-37,39] Tamsulosin is regarded as being safer with respect to cardiovascular side effects than earlier generation alpha-1-antagonists due to its uroselective nature.[45,49,50] The potential benefit of reduced incidence and duration of POUR, reduced morbidity associated with repeat intermittent catheterizations, reduced incidence of UTI, and reduced hospital length of stay outweigh the risks associated with administration of this medication.

The primary risk to human subjects taking tamsulosin in this study is postural or orthostatic hypotension, estimated to occur in 0.2% of patients taking the 0.4 mg daily dose of the drug. All patients will be regularly monitored with respect to blood pressure, heart rate, and rhythm according to existing standard postoperative procedures in place on the neurosurgical wards. Per the postoperative neurosurgery protocol, all patients are ambulated with the assistance of nursing staff until they are deemed safe for independent ambulation. Abnormal ejaculation was reported in 8.4% of patients taking the 0.4 mg daily dose. This risk should be minimal in the study given the short duration of time taking the study medication and decreased likelihood of sexual activity in the immediate postoperative period. There have been some reports of intraoperative floppy iris syndrome during cataract surgery while taking tamsulosin. Patients will be advised to avoid cataract surgery during the short time they are on the study medication. Allergic type reactions have been reported rarely. Patients will be informed as to the signs and symptoms of

allergic reactions. Priapism has also been reported as a rare risk (less than 1 in 50,000). Male patients will be informed about the seriousness of this condition.

Other adverse reactions include headache, dizziness, rhinitis, infection, asthenia, back pain, diarrhea, pharyngitis, chest pain, cough increased, somnolence, nausea, sinusitis, insomnia, libido decreased, tooth disorder, and blurred vision. Postmarketing experiences have also shown infrequent reports of dyspnea, palpitations, hypotension, atrial fibrillation, arrhythmia, tachycardia, skin desquamation including reports of Stevens-Johnson syndrome, constipation, and vomiting. All risks are taken directly from the official FDA drug information sheet.[16]

Patients experiencing possible severe side effects from this medication will be instructed to contact the primary neurosurgical team prior to hospitalization. During hospitalization, any patients experiencing such effects will be immediately evaluated by the neurosurgical team with appropriate intervention or consultation as deemed necessary. The PI or Co-PI will be informed of any serious adverse events thought to be related to medication administration and appropriate steps will be taken to determine whether the adverse event was related to the medication under investigation or other patient medication/condition (e.g. narcotic analgesics, other cardiovascular medication, or dehydration). The decision to stop the study medication will be determined by the primary neurosurgical team responsible for the patient in collaboration with the PI/Co-PI after the seriousness of the event is taken into consideration. All serious adverse events will be reported to the Mayo IRB within 24 hours of the event taking place, and to the FDA if necessary. All major and minor adverse effects of the study medication (tamsulosin or placebo) will be recorded in the medical record and used for data analysis.

Inclusion of Women, Minorities, and Children:

Women will be included in this study. Minorities will be included in the study in the same proportion as they present to the outpatient neurosurgery clinic. Mentally disabled patients, prisoners, and children will be excluded from the study.

References:

1. Lamonerie L, Marret E, Deleuze A, Lembert N, Dupont M, Bonnet F. Prevalence of postoperative bladder distension and urinary retention detected by ultrasound measurement. British journal of anaesthesia 2004;92:544-6.
2. Sarasin SM, Walton MJ, Singh HP, Clark DI. Can a urinary tract symptom score predict the development of postoperative urinary retention in patients undergoing lower limb arthroplasty under spinal anaesthesia? A prospective study. Annals of the Royal College of Surgeons of England 2006;88:394-8.
3. Toyonaga T, Matsushima M, Sogawa N, et al. Postoperative urinary retention after surgery for benign anorectal disease: potential risk factors and strategy for prevention. International journal of colorectal disease 2006;21:676-82.
4. Keita H, Diouf E, Tubach F, et al. Predictive factors of early postoperative urinary retention in the postanesthesia care unit. Anesthesia and analgesia 2005;101:592-6, table of contents.
5. Dreijer B, Møller MH, Bartholdy J. Post-operative urinary retention in a general surgical population. European journal of anaesthesiology 2011;28:190-4.
6. Zaheer S, Reilly WT, Pemberton JH, Ilstrup D. Urinary retention after operations for benign anorectal diseases. Diseases of the colon and rectum 1998;41:696-704.
7. Jensen P, Mikkelsen T, Kehlet H. Postherniorrhaphy urinary retention--effect of local, regional, and general anesthesia: a review. Regional anesthesia and pain medicine 2002;27:612-7.
8. Gönüllü NN, Gönüllü M, Utkan NZ, Dülger M, Gökgöz S, Karsli B. Postoperative retention of urine in general surgical patients. The European journal of surgery = Acta chirurgica 1993;159:145-7.
9. Boulis NM, Mian FS, Rodriguez D, Cho E, Hoff JT. Urinary retention following routine neurosurgical spine procedures. Surgical neurology 2001;55:23-7; discussion 7-8.
10. Dobbs SP, Jackson SR, Wilson AM, Maplethorpe RP, Hammond RH. A prospective, randomized trial comparing continuous bladder drainage with catheterization at abdominal hysterectomy. British journal of urology 1997;80:554-6.
11. Donovan TL, Gordon RO, Nagel DA. Urinary infections in total hip arthroplasty. Influences of prophylactic cephalosporins and catheterization. The Journal of bone and joint surgery American volume 1976;58:1134-7.
12. Leventhal A, Pfau A. Pharmacologic management of postoperative overdistention of the bladder. Surgery, gynecology & obstetrics 1978;146:347-8.
13. Tammela T. Prevention of prolonged voiding problems after unexpected postoperative urinary retention: comparison of phenoxybenzamine and carbachol. The Journal of urology 1986;136:1254-7.

14. Tammela T. Postoperative urinary retention--why the patient cannot void. Scandinavian journal of urology and nephrology Supplementum 1995;175:75-7.
15. Finkbeiner AE, Bissada NK. Drug therapy for lower urinary tract dysfunction. The Urologic clinics of North America 1980;7:3-16.
16. Food and Drug Administration Web Site, Tamsulosin Label Revision. July 2011. (Accessed 10/23//11, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020579s027lbl.pdf.)
17. Hedlund H, Andersson KE, Larsson B. Alpha-adrenoceptors and muscarinic receptors in the isolated human prostate. The Journal of urology 1985;134:1291-8.
18. Caine M, Pfau A, Perlberg S. The use of alpha-adrenergic blockers in benign prostatic obstruction. British journal of urology 1976;48:255-63.
19. Petros JG, Rimm EB, Robillard RJ, Argy O. Factors influencing postoperative urinary retention in patients undergoing elective inguinal herniorrhaphy. American journal of surgery 1991;161:431-3; discussion 4.
20. Petros JG, Rimm EB, Robillard RJ. Factors influencing urinary tract retention after elective open cholecystectomy. Surgery, gynecology & obstetrics 1992;174:497-500.
21. Petros JG, Bradley TM. Factors influencing postoperative urinary retention in patients undergoing surgery for benign anorectal disease. American journal of surgery 1990;159:374-6.
22. Kozol RA, Mason K, McGee K. Post-herniorrhaphy urinary retention: a randomized prospective study. The Journal of surgical research 1992;52:111-2.
23. Papavasiliou AK, Magnadottir HB, Gonda T, Franz D, Harbaugh RE. Clinical outcomes after carotid endarterectomy: comparison of the use of regional and general anesthetics. Journal of neurosurgery 2000;92:291-6.
24. Petros JG, Mallen JK, Howe K, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after open appendectomy. Surgery, gynecology & obstetrics 1993;177:172-5.
25. Ringdal M, Borg B, Hellström A-L. A survey on incidence and factors that may influence first postoperative urination. Urologic nursing 2003;23:341-6, 54.
26. Finkbeiner AE. Is bethanechol chloride clinically effective in promoting bladder emptying? A literature review. The Journal of urology 1985;134:443-9.
27. Bowers FJ, Hartmann R, Khanduja KS, Hardy TG, Aguilar PS, Stewart WR. Urecholine prophylaxis for urinary retention in anorectal surgery. Diseases of the colon and rectum 1987;30:41-2.
28. Eftaiha MS, Amshel AL, Shonberg IL. Comparison of two agents in prevention of urinary retention after benign anorectal surgery. Diseases of the colon and rectum 1980;23:470-2.
29. Barone JG, Cummings KB. Etiology of acute urinary retention following benign anorectal surgery. The American surgeon 1994;60:210-1.
30. Gönüllü NN, Dülger M, Utkan NZ, Cantürk NZ, Alponat A. Prevention of postherniorrhaphy urinary retention with prazosin. The American surgeon 1999;65:55-8.

31. Goldman G, Leviav A, Mazor A, et al. Alpha-adrenergic blocker for posthernioplasty urinary retention. Prevention and treatment. Archives of surgery (Chicago, Ill : 1960) 1988;123:35-6.
32. Goldman G, Kahn PJ, Kashtan H, Stadler J, Wiznitzer T. Prevention and treatment of urinary retention and infection after surgical treatment of the colon and rectum with alpha adrenergic blockers. Surgery, gynecology & obstetrics 1988;166:447-50.
33. Livne PM, Kaplan B, Ovadia Y, Servadio C. Prevention of post-hysterectomy urinary retention by alpha-adrenergic blocker. Acta obstetricia et gynecologica Scandinavica 1983;62:337-40.
34. Tammela T, Kontturi M, Puranen J. Prevention of postoperative urinary retention after total hip arthroplasty in male patients. Annales chirurgiae et gynaecologiae 1987;76:170-2.
35. Evron S, Magora F, Sadovsky E. Prevention of urinary retention with phenoxybenzamine during epidural morphine. British medical journal (Clinical research ed) 1984;288:190.
36. Boonsue P, Yuenyao P. The Effectiveness of Bladder Training with or without Medications in Relieving Bladder Dysfunction. 1995.
37. Cataldo PA, Senagore AJ. Does alpha sympathetic blockade prevent urinary retention following anorectal surgery? Diseases of the colon and rectum 1991;34:1113-6.
38. Kemp D, Tabaka N. Postoperative urinary retention: Part II--A retrospective study. Journal of post anesthesia nursing 1990;5:397-400.
39. Burger DH, Kappetein AP, Boutkan H, Breslau PJ. Prevention of urinary retention after general surgery: a controlled trial of carbachol/diazepam versus alfusozine. Journal of the American College of Surgeons 1997;185:234-6.
40. Bailey HR, Ferguson JA. Prevention of urinary retention by fluid restriction following anorectal operations. Diseases of the colon and rectum 1976;19:250-2.
41. Buckley BS, Lapitan MCM. Drugs for treatment of urinary retention after surgery in adults. Cochrane database of systematic reviews (Online) 2010:CD008023.
42. Dong Z, Wang Z, Yang K, Liu Y, Gao W, Chen W. Tamsulosin versus terazosin for benign prostatic hyperplasia: a systematic review. Systems biology in reproductive medicine 2009;55:129-36.
43. Reitz A, Haferkamp A, Kyburz T, Knapp PA, Wefer B, Schurch B. The effect of tamsulosin on the resting tone and the contractile behaviour of the female urethra: a functional urodynamic study in healthy women. European urology 2004;46:235-40; discussion 40.
44. Chang S-J, Chiang I-N, Yu H-J. The effectiveness of tamsulosin in treating women with voiding difficulty. International Journal of Urology 2008;15:981-5.
45. Hajebrahimi S, Azaripour, Sadeghi-Bazargani. Effect of tamsulosin versus prazosin on clinical and urodynamic parameters in women with voiding difficulty: a randomized clinical trial. International Journal of General Medicine 2011:35.
46. High Blood Pressure--Medicines to Help You. Food and Drug Administration. (Accessed 11/17/11, at http://www.fda.gov/forconsumers/byaudience/forwomen/ucm118594.htm.)

47. Alpha Blocker. Mayo Clinic. (Accessed 11/17/11, at http://www.mayoclinic.com/health/alpha-blockers/HI00055.)
48. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Food and Drug Administration. (Accessed 11/17/11, at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm - potency.)
49. Tsujii T. Comparison of prazosin, terazosin and tamsulosin in the treatment of symptomatic benign prostatic hyperplasia: a short-term open, randomized multicenter study. BPH Medical Therapy Study Group. Benign prostatic hyperplasia. International Journal of Urology 2000;7:199-205.
50. Buzelin JM, Fonteyne E, Kontturi M, Witjes WP, Khan A. Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction (symptomatic benign prostatic hyperplasia). The European Tamsulosin Study Group. British journal of urology 1997;80:597-605.