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COMBINATION VERSUS MONOTHERAPY WITH ALPHA-BLOCKERS AND ANTICHOLINERGICS FOR THE RELIEF OF URINARY STENT SYMPTOMS – A RANDOMIZED CONTROL TRIAL

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BACKGROUND AND SIGNIFICANCE

Ureteral stents are used to relieve acute or chronic obstruction of the upper urinary tract, or used as a prophylactic measure following instrumentation or surgery involving the ureter. Ureteral stents work by re-establishing or maintaining patency of the ureter in conditions of obstruction or injury. Stents passively dilate the ureter, allowing urine to flow both through and around the stent, and are indicated when there is ureteral obstruction with or without renal insufficiency, secondary to nephrolithiasis, malignancy, or other pathologic processes. Additionally, they can be used as a prophylactic measure after endoscopic procedures involving the ureter, or surgical repair of the ureter such as in ureteral anastomoses.

Unfortunately, despite their use since the late 60's, stent related symptoms are common in patients after stent insertion and continue to be a challenge to manage. Overall quality of life is impaired in 45% - 80% of patients with ureteral stents in place [1]. Stent related symptoms occur in up to 80% of patients following stent insertion. These include: storage urinary symptoms such as urinary frequency, urgency, nocturia, dysuria, hematuria, stent colic (flank/SP pain), and incomplete emptying or urinary incontinence. To date, various methods have been investigated and employed in an effort to alleviate these symptoms, from various stent designs to pharmacotherapy. With respect to pharmacologic management of stent symptoms, various agents have been investigated, including intravesical pharmacologic therapy [2], periureteral injection of botox [3], selective alpha-1 blockers [4], and anticholinergic agents [5].

There are several studies documenting the evidence supporting the use of alpha-blockers to reduce stent discomfort, including two recent meta-analyses [4,6]. These analyses demonstrated a significant benefit for using either tamsulosin or alfusozin in relieving symptoms. However, only a few studies have assessed the efficacy of anticholinergic agents in this context, despite the theoretical and anecdotal benefits of this class of drugs. The available literature on anticholinergic therapy for stent symptom relief do show benefits, e.g. in one study, tolterodine ER showed symptom improvement over placebo [7]. Data on combination therapy with both agents is even more limited and show mixed results, from no advantage to modest benefits in the combination arm [8,9]. There is also evidence that suggests tolterodine ER does not achieve maximum benefit upon initiation of the medication. Kaplan et al. found no difference in urinary symptoms between placebo and tolterodine ER at 1 week, however by week 4 of medication therapy tolterodine ER was significantly better than placebo at improving urinary symptoms.[10] There is no available literature on the effect of starting tolterodine ER prior to surgery to give maximum benefit of the medication prior to placement of a ureteral stent.

We plan to design our study in a manner that will address some of the methodological weaknesses of the aforementioned studies, and use the most commonly used alpha-blocking and anticholinergic agents and dosing: tamsulosin 0.4mg PO OD and tolterodine ER 4mg PO OD, respectively.

OBJECTIVES AND HYPOTHESIS:

We aim to show that the addition of Tolterodine ER to Tamsulosin will provide added benefits in ameliorating stent related symptoms in patients who have had unilateral placement of a ureteral stent for urolithiasis. This objective will be assessed by determining the mean difference in the urinary symptom index domain of the USSQ (the Urinary Stent Symptom Questionnaire), which is a validated tool used to assess stent symptoms[1]. We felt that a 15% further decrease in the index score in the experimental group, compared to the control group would represent a clinically significant improvement in urinary symptoms, based on the prior studies evaluating lower urinary tract symptoms in patients with stents. We hypothesize that combination therapy with Tamsulosin and Tolterodine ER will yield greater symptom relief than tamsulosin alone. In addition, we hypothesize that a longer duration of treatment of Tolterodine ER, 2 weeks prior to insertion of the stent, will yield greater symptom relief than initiation of Tolterodine ER after stent placement or tamsulosin alone.

RESEARCH DESIGN AND METHODS:

This is a prospective, double blind, randomized control trial.

STUDY SITE

This study was originally planned to take place at UW Health, Meriter Health Sciences, Vista Medical Center East and University of Manitoba. Three of the sites were unable to recruit patients to the study and have dropped out of the study: Meriter Health Sciences, Vista Medical Center East and University of Manitoba. Thus, the study was amended in 2014 to be a single site study conducted only at the UW Health.

The study site will obtain an IRB approval prior to recruiting any patients.

1. UW hospitals and clinics. Department of Urology, Madison, WI.
    - Study coordinator – Dr. Sara Best, & Dr. Stephen Nakada

STUDY ACTIVITIES

Patients who will be undergoing urinary stent insertion during the management of renal or ureteral stones, or other conditions requiring endoscopy will be randomized into the combination or monotherapy arm, based on a computer generated randomization scheme, and will be enrolled into the study arm in a blinded manner. The study is intended to be double-blinded. The drug kit will linked to the randomization number and both the investigator and patient will thus be blinded to the treatment. All patients will be required to provide a signed informed consent, which outlines the differences in the two treatment arms and study objectives. Patients will be provided the corresponding pills in pre-filled vials, based on their group assignment. Initially, the study used a 7-day treatment regimen. Patients in the monotherapy arm were given a set of Tamsulosin and placebo pills, while the combination therapy arm were given a set of Tamsulosin and Tolderodine ER, with sufficient quantities for 7 days. Pill counts were obtained at the end of the follow-up period to ensure compliance. All patients enrolled into the study were asked to complete the USSQ prior to stent insertion to serve as a baseline assessment of urinary symptoms, and again at 24 hours, 5 days after stent insertion and post stent removal. In the 7-day regimen, 80 patients were enrolled and completed the study (15 patients enrolled but withdrawn, 95 patients in total).

The data analysis shows no benefit from being on combination therapy likely secondary to the short duration of therapy.

In 2014, a change of protocol was approved that extended the study treatment to 21 days. Patients will start the study medication 2 weeks prior to their surgery date and continue for the 1 week duration of the stent. Patients in the monotherapy arm will be given a set of Tamsulosin and placebo pills, while the combination therapy arm will be given a set of Tamsulosin and Tolderodine ER, with sufficient quantities for 21 days. Pill counts will be obtained at the end of the follow-up period to ensure compliance. All patients enrolled into the study will complete the USSQ at baseline prior to starting medication to serve as a baseline assessment of urinary symptoms, prior to stent insertion, and again at 24 hours, 5 days after stent insertion and post stent removal. The patients will have the stent removed in 7 days, which will conclude the study period. If the stent needs to be removed sooner, it will be arranged as per current protocol. Early termination is only relevant if the 5 day USSQ is not completed. In the 21-day regimen, 106 patients are planned to be enrolled. Thus, a total of 201 patients, to see if there is a difference with the longer duration of medication treatment. Subjects have been enrolled on this 21-day regimen since 10/29/2014, and all new subjects use this regimen.

STUDY POPULATION

The key participants of this study will be male and female adult patients with kidney or ureteral stones, or other conditions, requiring unilateral or bilateral ureteral stent placement, either before or after a surgical intervention. Specifically, the post-operative

stent patients will include those who have undergone ureteroscopy, percutaneous nephrolithomy or extracorporeal shock-wave lithotripsy.

INCLUSION CRITERIA

Patients with unilateral or bilateral ureteral stent placement for urolithiasis are candidates for enrollment. These include: patients who have undergone ureteroscopy for renal or ureteral calculi, percutaneous nephrolithotomy (PCNL), shock-wave lithoripsy (SWL), or other conditions requiring stent placement post operatively, or for relief of pain or obstruction.

EXCLUSION CRITERIA

Candidates will be excluded from the study if ANY of the following apply:

1. Pre-existing LUTS
2. Active UTI
3. Contraindication to anticholinergic medication
    a. Prior hypersensitivity or allergy to tolterodine
    b. Patients with severe hepatic impairment (Child-Pugh Class C)
    c. Patients with uncontrolled close (narrow) angle glaucoma
    d. Patients with urinary retention
4. Current anticholinergic use
5. Chronic pelvic pain syndromes (e.g. acute/chronic prostatitis, interstitial cystitis)
6. Females who are pregnant or nursing
7. Under 18 years of age
8. Any patients unable to provide informed consent

PATIENT SCREENING AND RECRUITMENT

Potential subjects will be identified by the surgeon or study coordinator either at the time ureteroscopy, PCNL or stent placement is scheduled. These subjects will be screened for inclusion/exclusion criteria by reviewing their medical record. A waiver of patient screening is requested in the current application. If inclusion/exclusion criteria are met, the surgeon will ask the patient if he or she is interested in talking with a study team member for a study that he or she is eligible. One the patients' permission is obtained, a member of the research team will approach the patient for enrollment. Subjects will be recruited by verbal communication by the principal or co-investigators, or by a research coordinator. The patient must consent to participate as evidenced by the signed, study-specific, IRB-approved informed consent form before any study specific data may be collected and recorded.

We have requested a waiver of patient screening. We believe that the screening process will not pose more than minimal risks to subjects or adversely affect the rights and welfare of the subjects. The screening process only consists of reviews pre-existing data. No patient care or outcomes are affected as a result of screening. The surgeon or study coordinator will only review the medical record that is relevant for inclusion/exclusion criteria. No data will be collected in this phase. The exclusion criteria for the current study include pre-exsiting LUTS, active UTI, contraindication to anticholinergic medication, current anticholinergic use, chronic pelvic pain syndromes, pregnant females, and under 18 years of age. In the Urology clinic, a significant amount of patients who undergo stone

surgeries may have LUTS, active UTI, or currently taking anticholinergic medication. Consent without pre-screening will create a significant dropout rate. Thus, the study could not practicably be carried out without the waiver of screening.

Once appropriate informed consent has been obtained, a complete medical history including a detailed urologic history will be completed. The subject will be randomized to one of the two arms (tamsulosin + placebo versus tamsulosin + tolterodine) using a computerized randomization scheme.

STUDY DRUG/INTERVENTION

The study drugs of interest are Tamsulosin and Tolterodine ER, both of which are routinely used in urology. The UW pharmacy will supply the study drugs and placebo. Each of the study drugs and placebo will be provided in standard drug vials. Under the original, 7-day study treatment regimen, each vial contained 7 pills each. In 2014, the study was amended to add a 21-day treatment regimen. This replacement study will use only the 21-day treatment regimen, and the drug vials will contain 21 pills each. The placebo capsule will be similar in color and appearance to the Tolterodine capsule, and will be provided by the UW pharmacy. Patients may continue to use any prior medications concurrently with either of the study drugs, and no washout period is necessary.

TAMSULOSIN

Tamsulosin is a selective α_{1a}-blocker (Flomax™), generic since 2009. It is an antagonist of α1-mediated contraction of prostate, bladder and proximal urethral smooth muscle, and as such, reduces urethral pressure and resistance, bladder outlet resistance, bladder hyperactivity, and consequently LUTS. Its adverse effects include headache, dizziness, asthenia, nasal congestion, retrograde ejaculation, and a rare reversible condition known as floppy iris syndrome, which is only relevant if patients are undergoing cataract surgery.

TOLTERODINE ER

Toleterodine ER is an anticholinergic (antimuscurinic) agent, which is used as one of the first line agents for detrusor overactivity. It is given as once-daily dosing for overactive bladder symptoms, and even used in BPH patients exhibiting bladder symptoms. Its side-effects include xerostomia, xeropthalmia, gastroparesis, constipation, drowsiness, acute urinary retention, but unlike other drugs of this class, e.g. oxybutynin, tolterodine ER causes little to no cognitive impairment due to its larger molecular weight which precludes crossing of the BBB.

SAFETY AND MONITORING

Regular inquiries of study flow, pertaining to patient recruitment, randomization, patient compliance (with medication and completing questionnaires) and adverse events will be scheduled to occur after the first week and subsequently every two weeks during the active patient enlistment phase. Any adverse events/side effects will be monitored as per

standard protocol in clinical use. Patients will be instructed to report any untoward reactions to the study drugs to the urology clinic or on-call urology staff.

No significant adverse events are anticipated with either of the study drugs, as they are routinely used in everyday urology practice. The patient will report side effects if and when they occur; the drug will be stopped if continuation is deemed inappropriate. Any adverse events or unanticipated problems will be recorded and the offending drug will be stopped, and the patient counseled accordingly. If a patient has side effects that precludes their ongoing participation in the study, they will be withdrawn and considered a study drop-out. All measures will be in effect to prevent breaches of confidentiality and/or emotional upset.

Patients are instructed to contact their treating surgeon if they have symptoms that may require placing the stent or having surgery sooner than expected. The surgeons who perform these procedures are also members of the study team, and will ensure that all patients' clinical care will not be influenced due to study participation. We confirm that study participation will not delay needed clinical care in the event that an enrolled subject requires stent placement sooner than anticipated. We will only include patients whose stent placement will not be delayed as a result of study participation. If the patient has the stent placed in the interim or has discontinued medications, he or she will be excluded from the study.

STATISTICAL ANALYSIS & POWER CALCULATIONS:

In 2014, a change of protocol was approved that extended the study treatment to 21 days. Our sample size calculation in the 21-day regimen was based on the recommended sample size calculations by the original developers of the USSQ [1]. The authors' calculations were based on the results of their validation studies that compared mean domain score and standard deviation differences between stented and control patients, using a 2-tailed test ($p<0.05$). The percentage change (15%) translates to an absolute change in score by 4 points. Additionally, we extrapolated data from a recent meta-analysis evaluating the efficacy of tamsulosin to relieve stent related symptoms, which showed a mean standard deviation of 6.5 points between the tamsulosin and placebo arm [4] to confirm the previous authors' sample size. With an expected decrease of 4 points with the combination therapy, and an assumption of similar standard deviation (6.5), a two-tailed t-test ($p=0.05$) and power of 0.80, our calculation yielded 43 patients per arm. Given the relatively similar numbers from the two calculations, we opted to use the more conservative sample size of 53 patients per arm as the data collection endpoint.

We are assessing for both an absolute and relative change in the USSQ scores.

1. We will be assessing for a relative change of 4 actual points (which translates to a 15% change, as per Joshi et al's validation study) within each group from immediately post stent insertion at 24 hours compared to day 5.
2. We will also assess for a change in scores between groups, i.e. comparing the mean intra-group score change as described in 1 (i.e., immediately post stent insertion at 24 hours compared to day 5).

The questionnaire responses will be analyzed using cross tabulations and descriptive statistics to assess differences between groups. Paired *t*-tests will be used to assess within-group change in scores from the USSQ (comparison between post-op, i.e. at 48 hours, and day 5) and other discriminant properties. *T*-tests will be used to assess inter-group score changes.

The intent-to-treat principle will be employed in the event subjects have to withdraw from their assigned group, although this is not expected given that both treatment medications are used extensively in urology, and both treatment regimens are occasionally employed based on anecdotal physician experience.

DATA SECURITY:

All information obtained from the medical record and questionnaires will be kept secure and only accessible by the defined study personnel. Data collected will be stored into a Microsoft® Excel database by the research coordinator at the UW Hospitals site. All information will be de-identified and coded prior to database entry. The key for the code will be stored on a different computer for safety.

REFERENCES

1. Joshi HB, Newns N, Stainthorpe A, MacDonagh RP, Keeley FX, Timoney AG. Ureteral stent symptom questionnaire: development and validation of a multidimensional quality of life measure. *J Urol.* Mar 2003;169(3):1060-1064.

2. Beiko DT, Watterson JD, Knudsen BE, et al. Double-blind randomized controlled trial assessing the safety and efficacy of intravesical agents for ureteral stent symptoms after extracorporeal shockwave lithotripsy. *J Endourol.* Oct 2004;18(8):723-730.

3. Gupta M, Patel T, Xavier K, et al. Prospective randomized evaluation of periureteral botulinum toxin type A injection for ureteral stent pain reduction. *J Urol.* Feb 2010;183(2):598-602.

4. Yakoubi R, Lemdani M, Monga M, Villers A, Koenig P. Is there a role for α-blockers in ureteral stent related symptoms? A systematic review and meta-analysis. *J Urol.* Sep 2011;186(3):928-934.

5. Norris RD, Sur RL, Springhart WP, et al. A prospective, randomized, double-blinded placebo-controlled comparison of extended release oxybutynin versus phenazopyridine for the management of postoperative ureteral stent discomfort. *Urology.* May 2008;71(5):792-795.

6. Lamb AD, Vowler SL, Johnston R, Dunn N, Wiseman OJ. Meta-analysis showing the beneficial effect of α-blockers on ureteric stent discomfort. *BJU Int.* Dec 2011;108(11):1894-1902.

7. Park SC, Jung SW, Lee JW, Rim JS. The effects of tolterodine extended release and alfuzosin for the treatment of double-j stent-related symptoms. *J Endourol.* Nov 2009;23(11):1913-1917.

8. Lee SJ, Yoo C, Oh CY, et al. Stent Position Is More Important than α-Blockers or Anticholinergics for Stent-Related Lower Urinary Tract Symptoms after Ureteroscopic Ureterolithotomy: A Prospective Randomized Study. *Korean J Urol.* Sep 2010;51(9):636-641.

9. Lim KT, Kim YT, Lee TY, Park SY. Effects of tamsulosin, solifenacin, and combination therapy for the treatment of ureteral stent related discomforts. *Korean J Urol.* Jul 2011;52(7):485-488.

10. Kaplan SA, Schneider T, Foote JE, et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial, BJUI 107: 1432-1440.