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THE UNIVERSITY OF KANSAS HEALTH SYSTEM

Department of Urology

Investigator Initiated Trial

Use of Hyoscyamine versus Tamsulosin for Management of Ureteral Stent Irritation

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LIST OF ABBREVIATIONS (Examples)

SID	Study Identification
KUMC	University of Kansas Medical Center
U	Urine
S	Serum
T	Tissue
M	Month
HSC#	Human Subjects Committee #
USSQ	Ureteral Stent Symptom Questionnaire

1.0 STUDY SUMMARY

1.1 AIM AND HYPOTHESIS

The objective of this project is to compare the efficacy of hyoscyamine to tamsulosin monotherapy in treating lower urinary tract symptoms in patients with indwelling double-J ureteral stents.

Ureteral stents are routinely used in a variety of urologic conditions. Unfortunately, indwelling ureteral stents commonly cause significant pain and discomfort due to irritation to the urinary system. Many studies have looked at methods to reduce these uncomfortable symptoms ranging from altering stent designs to pharmacologic therapies attempting to alleviate stent-discomfort. However, stent-related discomfort continues to be an issue and is often the cause of their removal earlier than planned. While the efficacy of certain alpha blockers and anticholinergics in treating stent-related symptoms have been studied, the data for the use of hyoscyamine in this setting is lacking. A literature search yielded no studies evaluating the use of hyoscyamine in this setting to date. We hypothesize that hyoscyamine (brand name Levsin) is equivalent to tamsulosin in treating lower urinary tract symptoms in patients with indwelling double-J ureteral stents due to its anticholinergic properties. Furthermore, we hypothesize that patients in the hyoscyamine arm will not require additional pain medications (e.g. Pyridium, narcotics) to help control stent-related discomfort compared to the tamsulosin arm.

BACKGROUND AND RATIONALE

2.1 DISEASE BACKGROUND

Ureteral double-J stent was first described by Finney et al in 1978, and has since become a routine and indispensable urological tool used in a variety of conditions including obstructing kidney stones, obstructing ureteral or bladder masses, injury or trauma to the ureter or kidney, scarring in the ureter, or for masses in the pelvis that extrinsically compress the ureter.[1–3] Despite the usefulness of ureteral stents, patients experience uncomfortable stent-related symptoms including bladder spasms, pain, frequency, urgency, and as a result, an overall decrease in quality of life. Studies investigating the etiology of these symptoms found that the important factors contributing to stent discomfort include the pressure transmitted to the renal pelvis during urination, irritation to the trigone caused by the intravesicular curl of the stent, and spasms of ureteral smooth muscle due to the presence of a indwelling foreign object.[4] One study showed 80% of patients had stent related discomfort that interfered with their daily activities, which resulted in 32% of patients requesting the stent removed prematurely.[5] Many studies have

looked at improving these uncomfortable symptoms including using stents with tapering tails at the distal end[6], various stent coatings including Hydrogel and carbon[7,8], and pharmacological treatments with alpha blockers, anticholinergics and empirically prescribed analgesics.[9]

2.2 RATIONALE

Providers routinely prescribe alpha antagonists and/or anticholinergics to patients in order to relax the bladder and minimize the discomfort. Numerous studies have investigated the beneficial effect of alpha antagonists for ureteral stent-related discomfort. Tamsulosin is a selective α_{1a}-blocker that antagonizes α_1 mediated contraction of prostate, bladder and proximal urethral smooth muscle. Owing to this mechanism, it reduces urethral and bladder outlet resistance and decreases urinary reflux, ureteric motility and bladder hyperactivity, all of which work to alleviate stent-related discomfort.[10,11] Similarly, many studies have evaluated the utility of anticholinergics in treating stent discomfort since many of the stent-related symptoms are similar to overactive bladder symptoms caused by muscarinic receptor mediated involuntary bladder contractions.[12–15] Hyoscyamine is a prescription drug that became available before 1938 and is considered a 'Grandfather Drug.' Hyoscyamine is one of the least expensive anticholinergics on the market, and furthermore, it has more favorable pharmacokinetics compared to other anticholinergics that are typically prescribed for stent-related discomfort. Oxybutynin, for example, has an onset of action of 30 minutes to 1 hour with time to peak effect of 3 to 6 hours,[16] compared to Hyoscyamine which has an onset of action of 2-3 minutes with time to peak effect of 30 minutes to 1 hour.[17,18] Since stent-related discomfort can be aggravated with activity and typically presents in a waxing and waning fashion, the rapid acting therapeutic effects of hyoscyamine may provide tremendous relief for patients with indwelling stents. A review of literature in PubMed did not yield any studies evaluating the efficacy of hyoscyamine in the treatment of stent-related discomfort. Since we routinely use hyoscyamine to treat patients with ureteral stent discomfort, it would be interesting to know how effective hyoscyamine is when used in this setting. Given the well-published data on tamsulosin, we would like to conduct a formal study comparing the efficacy of hyoscyamine to tamsulosin for treating symptoms associated with ureteral stents as assessed by a validated questionnaire, the Ureteral Stent Symptom Questionnaire, and provide the first research-based evidence regarding the efficacy of hyoscyamine for the treatment of stent-related discomfort.

3.0 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

To evaluate the efficacy of hyoscyamine compared to tamsulosin in improving the lower urinary tract symptoms of patients with indwelling double-J ureteral stents as assessed by the validated Ureteral Stent Symptom Questionnaire (USSQ).

3.2 SECONDARY OBJECTIVE

To determine if there is a difference between the amount of additional medications needed to treat stent related discomfort between patients receiving hyoscyamine versus those that receive tamsulosin.

To determine factors contributing to patients needing additional medication for treatment of stent-related discomfort.

4.0 PATIENT ELIGIBILITY

4.1 INCLUSION CRITERIA

1. Patients must be 18 years of age or older
2. Patient must require placement of a ureteral stent(s), per standard of care, following routine urological procedures including, but not limited to, ureteroscopy, stone extraction, or management of upper tract transitional cell carcinoma
3. Patient must agree to abstain from other clinical studies during the study period

4.2 EXCLUSION CRITERIA

1. Patients younger than 18 years of age
2. Patients with chronic or pre-existing indwelling stents
3. Patients currently receiving anticholinergic or alpha blocker therapy
4. Patients with chronic opioid or analgesic usage
5. Patients with chronic pain syndrome or symptomatic benign prostatic hyperplasia
6. Patients with an active untreated urinary tract infection
7. Patients who are currently pregnant or nursing
8. Patients with allergies or contraindication to either tamsulosin or hyoscyamine
9. Patients on active chemotherapy
10. Patients currently receiving other investigational therapy
11. Patients who are unable to sign consent/answer questionnaire due to compromised mental capacity or language barrier (the questionnaire is not validated in other languages)
12. Patients who have a stent placed emergently for an obstructing stone or septic stone without immediate stone removal,

13. Any stents placed that will stay in for longer than 2 weeks, including patients who suffered a ureteral injury (Grade 2 or above) during the procedure that will be classified as a screen fail

4.3 WITHDRAWL/TERMINATION CRITERIA

Patients who do not undergo the placement of a ureteral stent following a routine urological procedure will be withdrawn from the study. If the patient was scheduled to undergo the stent placement and for any reason the plan changed or was cancelled that patient will be taken off the protocol and considered discontinued. The patient spot will be replaced and the study ID number will not be reused. This will allow the protocol to be completed once 94 patients have completed treatment based on statistical calculations from the Biostatistics department (below).

Patients will be allowed to withdraw from the study at any time. If a patient cancels permission to use their health information the research team will stop collecting any additional information about them moving forward. The research team may use and share information that was gathered before they received the patient's withdrawal. The entire study may be discontinued for any reasons without the patients consent by the investigator conducting the study.

5.0 STUDY PROCEDURES

5.1 SCREENING/BASELINE PROCEDURES

All patients who present to the University of Kansas Health System Urology clinic will be screened for participation in this study. Patients who present to the Kansas Health System Emergency Department needing urological consultation will also be screened for participation.

This an open-label, randomized, prospective study investigating the efficacy of hyoscyamine compared to tamsulosin for symptoms of stent irritation in patients undergoing routine urological procedures and requiring ureteral stent placement post-procedure. The patient would be assured that neither acceptance nor refusal would change their standard of care. The study medications are used routinely in our daily practice, and the patient would still be prescribed these medications if indicated regardless of participation in the study. Since prescribing these medicines is in our current standard of care, patients will not be withdrawn from standard of care by either participating or not participating in this study. Patients will be identified through standard of care procedures in the evaluation for the need for a ureteral stent. Routine labs (e.g. complete blood count, basic or complete metabolic panel, b-hCG, urinalysis and urine culture) and imaging will be obtained as per standard care at the provider's discretion based on the patient's history and physical exam. If a patient meets the study criteria, an informed consent will be obtained and the first Ureteric Stent Symptoms Questionnaire will be administered to establish baseline symptoms prior to the insertion of a ureteral stent.

5.2 STUDY IDENTIFICATION

Patient study identification (SID) will be created by the study team at the time the patient is consented and is enrolled in the study. SID will be the HSC# follow by number in chronological order. For example: HSC#-XXX.

5.3 STUDY PROCEDURES

To assess ureteral stent symptoms, we will be conducting the Ureteric Stent Symptoms Questionnaire (USSQ). The USSQ was created by Joshi et al as an instrument to measure stent-related morbidity. The USSQ has been validated as a reliable instrument to measure the impact of ureteral stents.[19] This validated questionnaire has been used in many previous studies regarding stent pain. In our study, the USSQ will be conducted prior to stent placement, on POD1, POD7 (or just prior to the time of stent removal if the removal occurs prior to day 7), and POD30. Basic demographic information, stent duration, stent size, stone location/size and obstructing vs. non-obstructing (if applicable), post stent insertion complications, drug diary information and questionnaire responses will be entered into a REDCap database for storage and analysis. The stent diameter will be 6Fr for all patients in the study. The appropriate stent length will be assigned to the patient based on cross sectional imaging. If cross sectional imaging is not available then stent length with be measured using a open-ended catheter to measure ureteral length. A small portion of these patients will be seen in the emergency department or while they are having an acute pain episode, so we expect that some of the pre-stenting questionnaires may not provide an accurate baseline for symptoms in these patients, hence the POD30 questionnaire will be obtained.

After informed consent is obtained, the patient will be prospectively randomized to either treatment arm in an open-label fashion using REDCap's randomization function to determine which therapy they will receive after stent placement. In the event that a patient does not find relief with their particular treatment arm, they will be permitted to receive additional narcotics or Pyridium. Should the patient continue to have unrelieved symptoms, treatment crossover is allowed since the study is designed in an intent-to-treat fashion.

The first arm is hyoscyamine 0.125 mg tab sublingual every 4 hours as needed for discomfort, and the second arm is tamsulosin 0.4mg tab orally daily. Both dosing regimens are standard prescription orders. Both medications are routinely used in our practice, so patients are not being exposed to new safety risks compared to non-study patients. Risks are reasonable, as the medications used in this study are already commonly used in our daily practice. Patients will be given contact numbers for the Urology Department should they have any adverse side effects or concerns. Hyoscyamine is an anticholinergic and can cause side effects including constipation, dry mouth, drowsiness, headache, or lightheadedness. Tamsulosin is an alpha blocker and can

cause side effects including dizziness, fatigue, nasal congestion, syncope and retrograde ejaculation. Patients who have taken alpha blockers are at risk for intraoperative floppy iris syndrome if they are going a cataracts surgery in the near future. Patients will be advised to immediately stop the medicine and seek medical care if they develop the rare but severe reactions of skin rash, swelling, confusion, irregular or fast heartbeat, eye pain, or hallucinations. As part of the standard treatment pathway for post-stent insertion, patients are also sent home with a narcotic pain medication to help with pain and discomfort. Our pathway is to prescribe all patients with 10 tabs of Norco 5/325 1-2 tabs po q6H PRN unless there are contraindications or allergies to this specific narcotic, in which case they are prescribed an alternative narcotic with Percocet 5/325 1-2 tabs po q6H PRN. Patients will be given a drug diary to document their usage of the study medications to ensure compliance. Patients will also document usage of additional prescription medications for stent discomfort, including their narcotic usage, so that this information can be tracked as well. Patients will stop drug diary at time of stent removal.

Questionnaires will be completed either in person if patient is in clinic or inpatient, or via a REDCap survey prior to stent placement, POD1, POD7 or at the time of stent removal if the removal occurs prior to day 7, and POD30. Patients with strings attach to stents will be included as there is no literature to suggest that strings cause additional stent irritation. Both medications will be stopped once the ureteral stent is removed as part of routine urological follow-up care for the primary etiology. Once the number of study participants reaches the pre-determined goal as calculated by our biostatistician, study enrollment will conclude and we will begin analyzing the data.

5.4 STUDY DESIGN AND SAMPLE SIZE

Total sample size: 100

The study will be conducted as a randomized comparative effectiveness trial with two arms. Subjects will be randomized to one of two treatments WITH either hyoscyamine or tamsulosin. Our hypothesis is that the hyoscyamine is at least as effective as tamsulosin in treating lower urinary tract symptoms. Symptoms will be quantified using the Urinary Symptom Index (USI) of the validated Ureteral Stent Symptom Questionnaire (USSQ). To address the hypothesis, the study will be conducted as a non-inferiority trial, following the hypothesis that hyoscyamine is not inferior to tamsulosin by more than a 15% margin in terms of the USI. The sample size was estimated using the PowerTOST package for the R statistical environment, based on a nominal power of 80% and an alpha-level of .025 for the one-sided t-test. Our null hypothesis is therefore that the mean USI for those treated with tamsulosin is more than 15% greater than those treated with hyoscyamine, so that by rejecting it, we may conclude hyoscyamine is not-inferior to tamsulosin by more than a 15% margin of USI for treating lower urinary tract symptoms. Furthermore, we assume that the coefficient of variation (CV) for the mean Urinary Index Score

will be similar to that in Park, et al.20 The CV in that study for the Urinary Symptom Index at week 2 after stent placement for the tamsulosin group was approximately .25. This is slightly higher, but similar to the CV of .22 for the USI in Maldonado-Avila, et al. which collected data at week 1, and therefore should be slightly conservative.21 Using these assumptions, we estimated that the sample size for each arm would need to be approximately 47, in order to have the desired power.

5.5 DATA ANALYSIS

The main hypothesis of the non-inferiority of hyoscyamine to tamsulosin for treating lower urinary tract symptoms will be tested using a t-test for non-inferiority of the change in USI between POD1 and POD7 (or day of stent removal if removed before day 7) in each treatment arm. This should be slightly more powerful than the t-test at POD7 alone that we used to estimate the sample size, but there are not enough data available for the distribution at POD1 in order to make a good estimate of the change. The non-inferiority margin will be 15% of the change in USI. The primary analysis will be conducted as intention-to-treat (ITT). That is, subjects will be analyzed as belonging to the arm they were randomized to, irrespective of later crossover or other modifications. This approach is in line with the current statement on Consolidated Standards of Reporting Trials (CONSORT).[22] Descriptive statistics will be used to describe the results from all USSQ domains at each timepoint (i.e. mean and standard deviation, along with confidence intervals for urinary symptom index, pain symptom index, etc.). We will also conduct non-inferiority tests of change in score for ITT with hyoscyamine versus tamsulosin for the other domains spanned by the USSQ, including pain symptom index, general health index, work performance index, and sexual matters between POD1 and POD7, although we may not be well-powered to detect non-inferiority for these additional domains.

The secondary goal of determining if there are differences in the amount of additional medications need to treat stent-related discomfort between treatment arms will be examined primarily through descriptive statistics. The drug diaries of all subjects will be used to tabulate the kinds and amounts of additional medications used. For each subject, the number of days that additional medications were used will be counted. The proportion of days that additional medications were used will be calculated for each group and 95% confidence intervals will be calculated.

Finally, we will also calculate the informed consent rate, and the discontinuation rate for those patients needing to be removed from the study in each arm.

In all cases, a p-value ≤ .05 will be taken as a statistically significant result.

5.6 SCHEDULE OF EVENTS

Visits	Enrollment	Stent Placement	POD1	POD2	POD3	POD4	POD5	POD6	POD7[A]	POD30
USSQ	X		X						X	X
Randomization	X									
Complete Medication Diary		X	X	X	X	X	X	X	X	
REDCap Survey			X						X	X
Stop Medication									X	

Footnotes: A = If stent is removed prior to day seven then USSQ will occur on day of stent removal and diary will be stopped. If stent is removed after day seven then USSQ will occur on day seven but the diary will be stopped on day of stent removal.

6.0 REGULATORY REQUIREMENTS

6.1 PROTOCOL REVIEW AND AMENDMENTS

The protocol, the proposed informed consent and all forms of participant information related to the study and any other necessary documents must be submitted, reviewed and approved by the University of Kansas Medical Center (KUMC) properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators. All decisions of the IRB concerning the conduct of the study must be made in writing. A yearly continuing review will also be submitted to the IRB.

6.2 Informed Consent

Any patient who is present a consent form that describes this study will be provided the most up to date consent form. The purpose of the consent form is provide sufficient information to the study participant in order to make an informed decision about their participation in the study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

Subjects will have time to ask any questions and will be given the opportunity to review the consent form in the absence of members of the study team prior to signing. Our team assures the informed consent process is an ongoing exchange of information between our research team and the study participants throughout the course of the research study. Patients who are interested in learning about participation in our trial will be introduced to a member of the study team who will then verbally explain the study in detail. Our process ensures respect for persons through provision of thoughtful consent for voluntary participation. Information will be presented in a manner that will enable the participant to voluntarily decide whether or not to participate as a research subject. Our procedures used in obtaining informed consent will educate the subject population in terms that they can understand. Therefore, our informed consent language and its documentation are written in "lay language" and presented in a way that facilitates understanding. It will be explained to the subjects that the study is voluntary and that they may discontinue at any time without prejudice. Subjects will have the opportunity to ask questions before signing the consent form. Subjects who agree to participate will be consented according to our institution's guidelines and in a private, closed-door setting. The consent document will be revised when deficiencies are noted or when additional information will improve the consent process. Informed consent will be documented by the use of a written, HSC-approved consent form and signed and dated by the subject or the subject's legally authorized representative. A signed copy will be given to the person signing the form. Consent forms, and all other study documentation, will be retained in accordance with the KUMC Research Records Retention Policy. This policy states, in part, that research records are to be retained by the investigator for a minimum of fifteen years.

Participation in the study is entirely voluntary. Subjects will have time to ask any questions and will be given the opportunity to review the consent form in the absence of members of the study team prior to signing (further details above).

Since potential subjects will be identified by their clinical care team during the course of routine care, the treating provider and care team will already have determined whether the subject is able to give informed consent prior to screening for participation.

6.3 ETHICS AND GOOD CLINICAL PRACTIVE (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice. All personnel will have completed all required GCP training. The study conduct will follow the ICH E6 Good Clinical Practice Guidelines. Along with the US Code of Federal Regulations (CFR). The conduct will follow all state, federal, local, and institutional laws, regulations, and policies.

It is understood that deviations from the protocol should be avoided, except with necessary to eliminate an immediate hazard to the research participant. In the instance of a deviation, it must be reported to the IRB according to the local reporting policy.

Out of window deviations will not be report to the IRB as they are not considered a risk/hazard to the patient.

7.0 PATIENT PROCEDURES

7.1 PATIENT REGISTRATION

Patient registration will occur at the time of consenting. Patients will be assigned a SID at time for consenting. Patient SID will be added to Velos(CRIS).

Patient demographics will be added to the redcap. All completed source documents for patient eligibility verification and registration will be kept in a study binder for monitoring and documentation purposes. Consenting process will also be documented.

8.0 STUDY MANAGEMENT

8.1 INVESTIGATOR FILESAND RETENTION OF DOCUMENTS

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified. Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinic charts, laboratory, ECG, signed ICFs, participant diaries, pathology reports and any other related documents. All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

8.2 CASE REPORT FORMS

Case report forms will be completed for each subject enrolled. All data will be entered and stored in a KUMC RedCap database. Only trained and approved personnel will have access to this database. Any source documents or additional research related items will be stored behind locked doors or on the R Drive within the study folder.

8.3 DATA MANAGEMENT AND SECURITY

The PI and research team will be responsible for handling the data and will allow study personnel to have access to study data within the KUMC REDCap database as necessary. Study data will be stored in a secure KUMC REDCap database. Permission will only be granted to trained and qualified study team members. Human subjects will be identifiable directly within the secure Velos(CRIS) system and information will be

kept in REDCap database (excluding MRN# and Names). Study team will be utilizing velos to link the patient with the study ID. This is a locked and secure database and only persons granted permission/access will be able to view this system. Data will be stored in Velos, RedCap, R Drive and within the Research Urology Offices.

Patient information from the medical record will be stored in a REDCap database outside of the medical record. Study team will abide by all HIPAA privacy laws and will do everything they can to ensure confidentiality of patients participation and information about sample collection, processing, storage, data, etc.

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