Study Title: A prospective double blind randomized control trial comparing the standard-of-care (SOC) prescription analgesic to an over-the-counter (OTC) analgesic protocol in managing postoperative pain after ureteroscopy with stent placement

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Background, Rationale and Context

Ureteral stent placement is one of the most frequent procedures that we as urologists perform, especially in the field of stones in the urinary tract. The term "stent" refers to a thin tube that we place within the lumen of the ureter to maintain its patency, permit healing or relieve an obstruction. The most common type of stent we use is the "double J stent," which was described in 1978 by Finney and has a proximal curl that is situated in the renal pelvis and a distal curl that is situated in the urinary bladder to keep the stent in place[1].

The current AUA/Society of Endourology guidelines published in 2016 state that it is reasonable to not stent patients after an ureteroscopy (URS) if they do not have a suspected ureteral injury, have no evidence of stricture or anatomic abnormality, have a normal contralateral kidney and normal renal function, and are not anticipated to need a second procedure[2]. But, truth be told, the majority of patients that undergo a URS end up with having a stent placed.

Despite their great value and common use in the field of urology, stents have several common side effects. These include infection, encrustation necessitating replacement, hematuria, stent pain and bothersome lower urinary tract symptoms (LUTS), which are estimated to affect at least 80% of patients who have an indwelling ureteral stent placed[3]. These symptoms include frequency, urgency, dysuria, incomplete emptying, flank pain, suprapubic pain, and incontinence.

There are several mechanisms that have been postulated as the cause of stent-related pain and voiding symptoms. The stent-related flank pain and renal colic can be secondary to reflux of urine through the stent during voiding, when intravesical pressures increase with contraction that transmits the increased pressures to the renal collecting system and ultimately resulting in flank pain[4]. There is also the issue of stent movement with patient's activity and stent position that are thought to be additional sources of pain and lower urinary tract symptoms due to direct irritation of the bladder mucosa[5,6].

One of the tools that has helped to standardize research on stent related complications is the ureteral stent symptoms questionnaire (USSQ) that Joshi and colleagues described in 2003[7]. This questionnaire consists of 38 items split into 6 sections: pain, voiding symptoms, work performance, sexual matters, overall general health, and additional problems.

Several medications have been tried and studied in an attempt decrease stent-related symptoms after placement. Nonsteroidal anti- inflammatory drugs (NSAIDs) and narcotic/opioid analgesics can be helpful for the pain, but do not have any impact on the voiding symptoms, for which the primary medications used are alpha-blockers and antimuscarinic and the AUA/Society of Endourology Guidelines lists providing these medications to patients to help reduce stent discomfort as a moderate recommendation with level B evidence[2].
In the United States, there is a known raging opioid abuse epidemic fueled by prescription medications and resulting in significant strain on our healthcare system. There is increasing evidence that prescribers are at least partly responsible for the opioid crisis because of overprescribing, in part due to the concern that uncontrolled pain after surgical procedures will result in poor patient satisfaction and increased workload for ancillary staff.[8]
Currently, there is a paucity of literature on analgesic requirements after URS for nephrolithiasis. It is critical that we as urologists and prescribers find a way to stop the needless overprescribing while still treating postoperative pain appropriately.
As such, efforts have recently begun to implement non-opioid protocols for outpatient urologic surgeries, but the majority of them retrospective.[9,10]

Our study objective is to evaluate the feasibility of a narcotic-free protocol in the management of postoperative pain after URS with stent placement and compare it to the current standard of care in our practice that does include opioids.

In our study, we propose to randomize 100 patients that undergo an outpatient URS for renal stones with stent placement into the two arms once being discharged, in a double blinded fashion, either with ibuprofen 400mg or Norco 5/325mg for pain management. Both being scheduled QID prn pattern until the stent will be removed in our clinic a week later. This type of study has never been performed before in the United States and could potentially change treatment patterns for this common problem.

Objectives

1. Primary Objective – To determine that a non -narcotic/opioid protocol for pain management can be implemented for URS outpatient stented patient population common to the United States.
2. Secondary Objective – To compare number of visits to the ED for postoperative genitourinary symptoms and pain, monitor number of telephone calls to the clinic, and requests for prescription pain medication refills of opioid Vs. non-opioids discharged patients.

Methods and Measures

Design

This will be a randomized double blinded control trial with subjects randomized to either the WFBH Urology practice's standard of care pain-relief narcotic/opioid group (Norco 5-325 mg) or an available over-the-counter non-opioid group (Ibuprofen 400 mg). Patients will be enrolled who are seen in the Urology Clinic at 140 Charlois Blvd. Those subjects with a renal stones who are consented for a ureteroscopy will be eligible for the study. Subjects eligible for the study will have a discussion with the study team member about their treatment options. They will be told

that the standard of care analgesic that is provided to patients undergoing ureteroscopy with stent placement is Norco. They will be informed that if they choose to take part in the study they will be randomized to receive the SOC medication (Norco), or they may receive OTC Ibuprofen which is a nonsteroidal anti-inflammatory medication. They can either elect not to be in the study and actively choose which treatment they would like, or they can choose to enter the study and be randomized to one of these treatment arms.

If the subject chooses to be enrolled in the study, they will sign the consent form for participation, as well as surgical consent form for URS. Randomization will be performed by the Investigational Drug Study pharmacy on the 10th floor of the Cancer Center and will occur prior to the surgical date chosen by the surgeon and the patient. Randomization will be performed using a random number generator.

The URS will be performed using standard of care instruments and techniques. No changes to operative technique will be performed for subjects in the study vs regular patients undergoing the same procedure. Post operatively; we plan to discharge all subjects home from the recovery unit. Hospital pharmacy will coat and prepare the generic medication and distribute the medication to the patients before they are discharged from the outpatient PACU.

All subjects will be seen one week after surgery for follow up, questioner filling and stent removal. At that point the remaining study medication will be returned as will information about ED visits and pain medication refilled will be collected as well.

Setting

Surgery will be performed at an academic medical center. All follow up care will be performed at the urology outpatient clinic.

Subject selection criteria

- **Inclusion Criteria**
  Ureteroscopy performed for renal stones
  Age over 18 years
  Two kidneys
- **Exclusion Criteria**
  Solitary Kidney
  Poor kidney function (GFR<30)
  Allergy to either Ibuprofen or Norco
  Pelvic Kidney
- **Sample Size**
  100 Patients with the plan to enroll 50 patients in each group.

Interventions and Interactions

All subjects enrolled in the study will be randomized to either narcotic/opioid or non-opioid management of postoperative pain after their stones treatment. The date of treatment will be decided between the subject and the treating surgeon. All treatments will be performed using the standard of care and will be performed in the same fashion as procedures for patients not enrolled in the study. There is no modification of the techniques used to remove the stones.

Post operatively, we plan to discharge all subjects home from the recovery unit with their designated coated pain medication supply for 7 days as well as usual scripts for alpha blockers and anti-muscarinic medication usually dispensed for LUTS. All subjects will be seen one week after surgery for follow up, collection of the remaining study medication, review of ED visits and pain medication refills, questioner filling and stent removal.

Outcome Measure(s)

The primary outcome will be the amount of pain medication used in each treatment arm and the need for additional pain medication and refills. Secondary outcomes will be needed ED visits, phone calls to clinic and symptoms evaluation using a validated questioner filled during their clinic visit.

Analytical Plan

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

Human Subjects Protection

Subject Recruitment Methods

There will be no active recruitment of subjects. All subjects will be identified based on referrals to the urology outpatient clinic. All patients with renal stones appropriate for a ureteroscopy will be eligible for the study.

Subject confidentially will be maintained by keeping all physical consent forms in a locked drawer in a locked office in Wattlington Hall. All electronic data will be maintained on a password secured computer in the hospital. This study does not require the transmission of an PHI to any entity outside the study team. No record of the study will be placed in the medical record so nobody outside the study team will know that the patient will be enrolled in the study.

All data and documents related to the study will be destroyed 36 months after completion of the study.

Informed Consent

Signed informed consent will be obtained from each subject. Consent will be obtained by a member of the study team. Consent will be obtained during the initial clinic visit at the urology outpatient clinic.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to

designated study personnel. Following data collection subject identifying information will be destroyed after 36 months, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References

1. Finney RP. Experience with new double J ureteral catheter stent. J Urol. 1978 Dec;120(6):678-681.
2. Assimos D, et al. Surgical management of stones: American urological association/endourological society guideline. J Urol. 2016;196(4):1161–9
3. Joshi HB, Okeke A, Newns N, Keeley FX Jr, Timoney AG. Characterization of urinary symptoms in patients with ureteral stents. Urology. 2002 Apr;59(4):511-516.
4. Mosli HA, Farsi HMA, al-Zimaity MF, Saleh TR, al-Zamzami MM. Vesicoureteral reflux in patients with double pigtail stents. J Urol. 1991;146(4):966–969.
5. Chew BH, Knudsen BE, Nott L, Pautler SE, Razvi H, Amann J, et al. Pilot study of ureteral movement in stented patients: first step in understanding dynamic ureteral anatomy to improve stent comfort. J Endourol. 2007;21(9):1069–75.
6. Al-Kandari AM, et al. Effects of proximal and distal ends of double-J ureteral stent position on postprocedural symptoms and quality of life: a randomized clinical trial. J Endourol. 2007;21(7): 698–702.
7. Joshi HB, et al. Ureteral stent symptom questionnaire: development and validation of a multidimensional quality of life measure. J Urol. 2003;169(3):1060–1064.
8. Theisen K, Jacobs B, Macleod L, Davies B. The United States opioid epidemic: a review of the surgeon's contribution to it and health policy initiatives. BJU Int. 2018 Nov;122(5):754-759.
9. Large T, Heiman J, Ross A, Anderson B, Krambeck A. Initial Experience with Narcotic-Free Ureteroscopy: A Feasibility Analysis. J Endourol. 2018 Oct;32(10):907-911.
10. Sobel DW, Cisu T, Barclay T, Pham A, Callas P, Sternberg K. A Retrospective Review Demonstrating the Feasibility of Discharging Patients Without Opioids After Ureteroscopy and Ureteral Stent Placement. J Endourol. 2018 Nov;32(11):1044-1049.

Appendix

1. Consent form
2. Ureteral stent symptoms questionnaire (USSQ)