Study Title: Double-blind, Placebo-controlled Randomized Controlled Trial of NSAID Prior to Ureteral Stent Removal in a Pediatric Population
PI: Jeffrey Campbell
Investigators: Alan Bielsky, Duncan Wilcox, Nicholas Cost, Vijay Vemulakonda,
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Protocol

Hypothesis and Specific Aims

We hypothesize that children who have a temporary, indwelling ureteral stent as part of care received during surgical treatment for either urolithiasis or ureteropelvic junction obstruction will experience a significantly smaller increase in post-operative pain if given a non-steroidal anti-inflammatory (NSAID) prior to removal of the ureteral stent when compared to placebo. We hypothesize that the incidence of severe post-stent removal pain is similar to an adult population. We aim to randomize patients who have an indwelling ureteral stent to either placebo or NSAID in a 1:1 ratio at least 15 minutes prior to the scheduled removal of the stent and compare pre-operative and post-operative (24 hours) pain scores to examine our primary and secondary outcomes.

Background and Significance

Ureteral stents are commonly used after treatment of urolithiasis and after surgical repair of ureteropelvic junction obstruction.[1] These stents can be very bothersome, affecting more than 80% of patients. This can result in increased flank and loin pain, dysuria, urinary frequency, even prompting unexpected emergency room visits.[2,3] In some rare circumstances, the discomfort may be so great as to require intravenous narcotics, unplanned admission or even emergent procedures to remove or replace the offending ureteral stent. Medications such as α-blockers (e.g., tamsulosin) have been previously shown in multiple studies to ameliorate some of this effect while the stent is *in situ*.[4,5] Despite its use, however, patients often continue to experience some discomfort and decreased quality of life.

Urologists have long commented on the anecdotal evidence that some patients experience severe, debilitating pain in the period following stent removal.[6,7] While some have hypothesized that stent size and positioning may influence symptoms while the stent is in place, the physiologic mechanism behind pain *after* removal of the foreign body from the ureter is not well-understood. *In vitro* and *in vivo* studies have demonstrated ureteral spasm, which may cause the discomfort felt by patients. Spasm has been shown to be partially mediated by the generation of prostaglandins and hence blocked by cyclooxygenase (COX) inhibitors like NSAIDs. [8-10]

Recently, a small double-blind placebo-controlled randomized controlled trial of a COX-2 inhibitor (felt to have better selectivity in the ureter) given to adults prior to outpatient stent removal in the urology clinic was completed.[11] 22 patients were randomized, and demonstrated significant reductions in severe pain reported in the 24 hours after surgery ($p < 0.01$). 55% of patients in the placebo arm reported pain scores ≥ 7 out of 10 versus zero patients in the intervention arm. Patients reporting severe pain in the placebo arm reported a mean 8.19 mg opioid medication use in the 24 hours after stent

removal whereas only 1.67 mg was used in the COX-2 inhibitor group (p = 0.03). No adverse events were reported.

Prior to this study, no known interventions were used specifically to reduce “post-stent syndrome,” as some have termed the phenomenon.[12] For pediatric patients with an indwelling ureteral stent, outpatient awake cystoscopy to remove a stent is not tolerated. As such, we typically bring patients to the operating room for a brief general anesthetic to allow for removal of a stent. At the termination of the procedure, intraurethral 2% viscous lidocaine is used (4 mg/kg or 0.2 mL/kg of 2% lidocaine up to maximum of 10 mL).[13] Virtually all patients receive a general anesthetic, and the use of NSAIDs pre-, intra-, or post-operatively is rare and inconsistently applied. These patients are instructed to take tamsulosin (an α-blocker) up to the day of their planned stent removal and then stop the medication. Afterwards, we generally instruct patients to alternate between acetaminophen and an NSAID (e.g., ibuprofen, a non-selective COX-1 and COX-2 inhibitor) as needed for any discomfort. No narcotics are typically prescribed. The incidence of “post-stent syndrome” in children is unknown.

Pain is difficult to objectively measure, particularly in children. Fortunately, there is a fair amount of research into various pain scales. The two we plan to use for this study include the Faces Pain Scale – Revised (FPS-R) or the visual analogue scale (VAS) depending on age. The FPS-R will be administered to children between 4 and 8 years of age, and the VAS will be given to patients between 9 and 18 years of age. Each of these scales has been validated and shown to be highly reproducible between individual patients. The FPS-R includes a series of faces indicating level of pain.[14] Standardized instructions are provided to the patient, and he or she is asked to indicate which face corresponds to his or her pain level. For older children (9 to 18 years of age), the VAS is a single line 100 mm long.[15] The patient is asked to place a mark somewhere on the line, with the left end representing no pain and the right end representing maximal pain. The distance from the left side is measured with a ruler and rounded to the nearest centimeter (0-10). Given the wide range of ages, younger children have difficulty conceptualizing the VAS system. Fortunately, the two scales have been shown to be interchangeable.[16]

“Post-stent syndrome” remains real and its incidence in the pediatric population remains unknown. Our study will be the first to investigate the incidence of this problem in patients undergoing planned stent removal and also determine the effectiveness of prevention using a non-selective NSAID that is safe and commonly used in children (ibuprofen).

Preliminary Studies/Progress Report

No studies regarding prevention of post-stent removal pain have been conducted in children. Our study design is based on the double-blind placebo-controlled randomized controlled trial by Tadros et al published in 2013 that studied the phenomenon in adults.[11] This study, as noted above, found a 55% incidence of severe pain in the 24 hours after stent removal in patients that received a placebo. Severe pain was defined as a VAS score ≥ 7 at any point during the post-operative period.

Research Methods

Outcome Measure(s)

Primary outcome:

> We hypothesize there will be at least a 75% reduction in post-operative severe pain (pain score ≥ 7) in patients receiving ibuprofen compared to those receiving placebo.

Secondary outcomes:

- Incidence of “significantly worsening” pain, defined as any increase ≥ 2 between the pre-operative and post-operative pain scale assessments for each patient
- Decreased incidence of “significantly worsening” pain, defined as any increase ≥ 2 between the pre-operative and post-operative pain scale assessments in those receiving NSAID versus placebo
- Incidence of “severe” pain during post-operative period, defined as any absolute score ≥ 7 on the post-operative pain scale assessment in the placebo arm
- Smaller increase in from pre- to post-operative pain score in those receiving NSAID versus placebo
- Decreased opioid usage post-operatively recorded in equivalents to milligrams intravenous morphine in those receiving NSAID versus placebo

Description of Population to be Enrolled

We plan to enroll pediatric patients between the ages of 4 and 18 who have received and completed surgical care for either upper tract urolithiasis (nephrolithiasis or ureterolithiasis) or ureteropelvic junction obstruction requiring an indwelling ureteral stent who consent to randomization to receive either liquid ibuprofen or liquid placebo prior to stent removal. Inclusion criteria include: unilateral ureteral stent for treatment of urolithiasis or ureteropelvic junction obstruction with planned outpatient surgical procedure removal under light sedation or general anesthesia. Exclusion criteria include: patients undergoing other concomitant surgical procedures at time of ureteral stent removal, patients with bilateral stents, patients with complicated stent removal (encrustation requiring ureteroscopy and/or laser lithotripsy, proximal migration of ureteral stent), pregnant patients, patients with developmental delay who are unable to report pain scores, patients with contraindications to receive NSAIDs (documented or stated allergy to NSAIDs, chronic kidney disease, prior renal transplantation, history of nasal polyps, history of asthma).

Study Design and Research Methods

This will be a double-blind, placebo-controlled, prospective randomized controlled trial comparing a weight-based dose of liquid ibuprofen (10 mg/kg orally x 1 up to a maximum of 400 mg) to a similar-tasting and appearing liquid placebo of equal volume. Patients will be assessed for eligibility pre-operatively using the stated inclusion and exclusion criteria. Patients who are deemed eligible and agree to be enrolled will be consented for enrollment by a study investigator. A separate assent will be obtained for

children between the ages of 7 and 12, while children between the ages of 13 and 17 will be able to confirm assent on the main parental consent form. Those who are deemed ineligible or refuse enrollment will be excluded and reasons for exclusion recorded in the study database along with demographic data.

The patient will fill out a pain questionnaire (with the assistance of a study investigator), which included either the Faces Pain Scale – Revised (FPS-R) or the visual analogue scale (VAS) depending on age. The FPS-R will be administered to children between 4 and 8 years of age, and the VAS will be given to patients between 9 and 18 years of age. Study investigators will record pain medications taken in previous 24 hours, record the last dose of tamsulosin, and review potential medication adverse effects. We will provide a similar pain questionnaire to be filled out in 24 hours (i.e., the day after surgery) with a addressed and stamped envelop to be returned to study investigators.

Patients who consent to enrollment will be randomized in a 1:1 ratio between liquid ibuprofen and placebo to be administered in the pre-operative area no fewer than 15 minutes prior to going back to the operating room for induction of anesthesia and stent removal. Randomization to either liquid ibuprofen or similar looking and tasting liquid placebo of similar consistency will be performed by the research pharmacy, who will stratify by age, sex and indication for stent to ensure balance in the two arms of the study. Investigators and patients will be blinded to the randomization scheme and medication identity until study termination. When a patient is enrolled, an order will be placed in the computer for the study drug, the pharmacy will perform the randomization and determine which medication (ibuprofen versus placebo) to prepare in the proper dose. Study medication will be sent to the pre-operative area and administered by a nurse and documented. Study medication will only be given after completion of the pre-operative questionnaire noted above.

Cystoscopy and stent removal will occur per standard of care under a short general anesthesia. Stent size, brand, and sidedness will be recorded. Cystoscopy will be performed with an age-appropriate sized scope to minimize discomfort per usual care. Scope size and configuration will be recorded. No opioid or NSAID medications will be given per usual practice. At the conclusion of the case, a weight-based dose of 2% viscous lidocaine (4 mg/kg up to maximum of 200 mg or 0.2 mL/kg up to maximum of 10 mL) will be given intraurethrally per usual care. Post-operatively, we will instruct patients to take acetaminophen and/or ibuprofen in weight-based dosing per normal routine. Our instructions specify they should start with acetaminophen (10 mg/kg oral dose up to a maximum of 500 mg) three hours after study medication was administered pre-operatively and proceed to an appropriate dose of ibuprofen (10 mg/kg oral dose up to a maximum of 400 mg) three hours thereafter, alternating between the two. All post-operative medications are to be taken only as needed, per usual practice, as long as there are no contraindications to their administration (acetaminophen: liver disease or liver failure; ibuprofen: documented or stated allergy to NSAIDs, chronic kidney disease, prior renal transplantation, history of nasal polyps, history of asthma).

Urology nurses typically call patients the day after surgery to review how a patient is doing and answer any questions. For study patients, we will use this call to also instruct parents on how to have the patient fill out the pain questionnaire and gather details on

pain medication usage post-operatively, determine whether the patient required a visit to the emergency room or hospital admission, and screen for any adverse effects from study medication administration (see listing of potential adverse effects below). We will review the records of patients admitted to the hospital and will record additional medications and interventions.

Description, Risks and Justification of Procedures and Data Collection Tools

Ibuprofen (a member of the NSAID class of medications) is commonly-used in children and is well-tolerated with minimal side effects. Its use is contraindicated in patients with kidney disease given its metabolism and clearance by the kidneys. Less commonly, it is contraindicated in patients with asthma, kidney transplantation, nasal polyps, or documented allergy to NSAIDs. Our exclusion criteria specifically forbid enrollment of patients in this study who have such contraindications. For those that are enrolled, we plan to warn patients and families regarding common and more rare side effects of ibuprofen. Common side effects include rash, nausea, dizziness, GI upset. Rare side effects include ringing in ears, itchiness, water retention, vomiting, diarrhea, mood changes, headache, blurred vision, double vision, bronchospasm, kidney failure. We will screen for these manifestations 24 hours after stent removal during the nursing call.

Adverse events will be reported to Dr. Bielsky, who will act as independent safety monitor, to determine need for follow up actions and record such events prospectively as they occur. Dr. Bielsky, as safety monitor, may require access to pharmacy records to determine the nature of the medication administered according to the severity of any adverse events, which we do not anticipate. He will not participate in the data collection or analysis at the conclusion of the trial, maintaining a double-blind methodology.

Given ibuprofen is usually recommended to be taken as needed after stent removal in these patients, giving the medication pre-operatively poses little foreseeable risk to the patient. We view randomizing patients to ibuprofen versus placebo with resumption of standard of care after stent removal as a low-risk study with large potential benefit if we are able to demonstrate ability to prevent post-stent syndrome pain and measure its baseline incidence (in the placebo arm).

The data collection sheet provides a listing of data points we plan to gather for study patients. A minimum of demographic data will be collected on patients who are excluded or refuse to be included in the study. This will allow comparison of patients included to those excluded to examine for possible sources of bias. The data points provide all the necessary information to account for potential confounders and variables that may or may not contribute to the outcome measures we seek.

Potential Scientific Problems

We can identify several potential confounders in this study, including use of other pain medications or use of an α-blocker that may influence patient outcomes. We have designed this protocol to account for usage of these medications. Usage of different scopes for patients of different ages may account for some small differences in perceived discomfort around the time of stent removal. We will record the size of the scope used. Other variables that may influence the primary or secondary outcomes

include stent size, stent duration, and indication for stent placement. These variables will all be recorded so as to evaluate their possible effect on outcomes, if any.

We have performed a power analysis as described below in an attempt to determine how many patients will be required to be randomized to answer our primary outcome. This power analysis is partly based on the Tadros et al randomized controlled study in adults. We have chosen a similar primary outcome, one we feel is suitable to our population and used the data from the adult population to derive the number of study participants we feel will provide adequate power. There is a chance we will not have enough power to adequately determine the primary outcome. Additionally, unlike in adults where stent removal is done awake, pediatric patients are given general anesthesia. This could attenuate the effect seen in adults. There is no accurate mechanism by which to predict whether such an effect might occur. Our study will make light of this, regardless of whether we are able to accept or reject our stated hypothesis.

Pain-related outcomes are very patient-specific and difficult to compare between patients, particularly raw or absolute scores. The Tadros et al study used an absolute cut-off of ≥ 7 to denote severe pain.[11] This study can be criticized for using such an absolute cut-off as part of one of their intended outcomes because one patient's "7" may not be the same as another patient's "7." Although comparing pre- and post-operative pain assessments for the same patient would offer greater internal validity, much larger sample sizes than are practical are necessary to detect even small changes. Other studies have shown that changes of even one point on a 10-point pain scale can be considered clinically significant, but poses the problem of requiring a large number of patients be randomized in order to detect that difference as statistically significant.[17]

Our study is designed to include children as young as 4 years old who can self-report pain. We felt in designing this study that including younger patients was important. As such, we must use two different pain scales, as they are designed and have been validated in different age groups. The results for both scales are reportable from 0 to 10. Comparison of the two scales demonstrate strong interscale correlation ($r = 0.93$, $p < 0.001$).[14] We feel the use of two different instruments will not be a significant source of bias. For comparison to the Tadros et al study, which did use absolute pain score ≥ 7 on the post-operative pain assessment as a study outcome, we will track incidence of "severe pain" and determine whether there is decreased incidence of this definition.[11]

Data Analysis Plan

Sample size estimation is based on primary outcome taking Tadros et al study results as reference without modification. A sample size of 20 patients from NSAID group and 20 patients from placebo group achieve 80% power ($\beta = 0.80$) to detect a 75% reduction in the baseline 55% incidence of severe pain on the post-operative pain assessment (two-sided test, $\alpha = 0.05$).

At the conclusion of the study, study investigators will be unblinded as to medication assignment at time of randomization. Randomization factors such as age, sex will be examined between groups, should imbalance exist between groups, these factors will then be adjusted as covariate in regression models. In addition, potential confounders, such as α-blocker use will also be adjusted in the model.

The placebo and NSAID groups will first be compared using the two-sample t-test for continuous data, Chi-Square test or Fisher's exact test for binomial data, and paired t-test for FPS-R or VAS pain score data obtained pre- and post-operatively. Results will be considered significant at $p < 0.05$. The data will be used to determine results with respect to the above-stated primary and secondary outcomes. General linear regression, logistic regression may be used to analyze the data if necessary.

Summarize Knowledge to be Gained

From this study, we will learn the true incidence of post-stent removal pain experienced by pediatric patients and will learn whether NSAIDs given *prior* to ureteral stent removal can prevent such pain and discomfort from occurring. If there is a similarly strong effect by NSAIDs similar to that shown in adults, it will greatly reduce at least one aspect of the discomfort regarding stents in this vulnerable population. Such information will be invaluable in counseling future patients who require ureteral stents, and if our hypothesis is correct, improve care and quality of life for these patients.

References

1. Smaldone MC, Corcoran AT, Docimo SG, et al: Endourological Management of Pediatric Stone Disease: Present Status. *J Urol* 2009; **181**: 17–28.

2. Joshi HB, Stainthorpe A, MacDonagh RP, et al: Indwelling Ureteral Stents: Evaluation of Symptoms, Quality of Life and Utility. *J Urol* 2003; **169**: 1065–1069.

3. Pryor JL, Langley MJ and Jenkins AD: Comparison of symptom characteristics of indwelling ureteral catheters. *J Urol* 1991; **145**: 719–722.

4. Yakoubi R, Lemdani M, Monga M, et al: Is There a Role for α-Blockers in Ureteral Stent Related Symptoms? A Systematic Review and Meta-Analysis. J Urol 2011; **186**: 928–934.

5. Nazim SM and Ather MH: Alpha-Blockers Impact Stent-Related Symptoms: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Endourol* 2012; **26**: 1237–1241.

6. Nair R, Drinnan NRT and Symes A: A single dose of a non-steroidal anti-inflammatory drug (NSAID) prevents severe pain after ureteric stent removal: a prospective, randomised, double-blind, placebo-controlled trial. *BJUI* 2013; **111**: E265–E266.

7. Garg M, Singh V and Sankhwar SN: A single dose of a non-steroidal anti-inflammatory drug (NSAID) prevents severe pain after ureteric stent removal: a prospective, randomised, double-blind, placebo-controlled trial. *BJUI* 2013; **112**: E1–E2.

8. Dellis A, Joshi HB, Timoney AG, et al: Relief of Stent Related Symptoms: Review of Engineering and Pharmacological Solutions. *J Urol* 2010; **184**: 1267–1272.

9. Wen CC, Coyle TLC, Jerde TJ, et al: Ketorolac Effectively Inhibits Ureteral Contractility in Vitro. *J Endourol* 2008; **22**: 739–742.

10. Nakada SY, Jerde TJ, Bjorling DE, et al: Selective cyclooxygenase-2 inhibitors reduce ureteral contraction in vitro: a better alternative for renal colic? *J Urol* 2000; **163**: 607–612.

11. Tadros NN, Bland L, Legg E, et al: A single dose of a non-steroidal anti-inflammatory drug (NSAID) prevents severe pain after ureteric stent removal: a prospective, randomised, double-blind, placebo-controlled trial. *BJUI* 2012; **111**: 101–105.

12. Schuster TG, Russell KY, Bloom DA, et al: Ureteroscopy For The Treatment Of Urolithiasis In Children. *J Urol* 2002; **167**: 1813–1816.

13. Xylocaine 2% jelly (lidocaine hydrochloride). U.S. Food and Drug Administration 2004. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/08816s032lbl.pdf, accessed March 17, 2014.

14. Hicks CL, Baeyer von CL, Spafford PA, et al: The Faces Pain Scale – Revised: toward a common metric in pediatric pain measurement. *Pain* 2001; **93**: 173–183.

15. Bailey B, Gravel J and Daoust R: Reliability of the visual analog scale in children with acute pain in the emergency department. *Pain* 2012; **153**: 839–842.

16. de Tovar C, Baeyer von CL, Wood C, et al: Postoperative self-report of pain in children: interscale agreement, response to analgesic, and preference for a faces scale and a visual analogue scale. *Pain Res Manag* 2010; **15**: 163–168.

17. Powell CV, Kelly A-M and Williams A: Determining the minimum clinically significant difference in visual analog pain score for children. *Ann Emerg Med* 2001; **37**: 28–31.