BIOMEDICAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: Perioperative pregabalin as part of a multimodal treatment plan for pain after ureteroscopy with stent placement: a randomized, controlled trial

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Table of Contents

PROTOCOL SUMMARY AND/OR SCHEMA

We propose a clinical trial examining the use of perioperative pregabalin to decrease opioid usage after ureteroscopy with stent placement. Patients undergoing ureteroscopy with stent placement will receive either a single dose of 300 mg pregabalin PO or an identical placebo in the preoperative area. We will assess patient centered outcomes, specifically examining possible side effects as well as short- and long-term opioid sparing effects.

OBJECTIVES AND SCIENTIFIC AIMS

Primary Hypothesis

The use of perioperative pregabalin in ureteroscopy with stent placement will decrease the amount of perioperative pain experienced by the patient.

Secondary Hypotheses

We hypothesize that the use of the perioperative pregabalin in ureteroscopy with stent placement will:

- Have secondary benefits in the immediate post-operative period
- Decrease the proportion of patients receiving opioid prescription in the first 30 post-operative days
- Not decrease patient satisfaction with their procedure
- Not significantly increase the risk of adverse outcomes
- Decrease the risk of new persistent opioid use at 3, 6, and 12 months after surgery

Primary Endpoints

The primary endpoint will be the value on the visual analog scale of pain score supplied by the patient approximately one hour after reaching the post-operative area.

Secondary Endpoints:

Secondary endpoints include the following:

- Reported post anesthesia care unit (PACU) symptoms experienced
- Score on clock drawing test
- Number of unplanned contacts between the patient and the healthcare system within 30 days
- Reported satisfaction at 7- and 30-days post procedure
- Proportion of patients with new persistent opioid use at 3, 6, and 12 months after surgery

BACKGROUND AND STUDY DESIGN/INTERVENTION

The prevalence of urolithiasis is greater than 8% and increasing in the United States (US) [1]. There are several treatment options, including ureteroscopy (with or without laser lithotripsy), extracorporeal shock wave lithotripsy, and percutaneous nephrolithotomy. A recent study in California demonstrated that ureteroscopic treatment was employed in more than 40% of interventions [2], with some nationwide estimates up to 59% [3]. At least 300,000 stone interventions are performed yearly in the US on working age adults [4], thereby, there are at least 120,000 ureteroscopies. There are several other indications for ureteroscopy, including diagnosis of structural anomaly and diagnosis and management of ureteral and renal pelvic tumors.

Depending on the specifics of the procedure, it may be advisable to place a ureteral stent intraoperatively [5]. The most commonly used variety of stent is the double J stent [6], which has long been known to cause post-operative pain in around 80% of patients, as well as irritative symptoms in a sizeable portion [7, 8]. Approximately 12% of those undergoing ureteroscopy will have an emergency department (ED) visit in the first 30 post-operative days [9], typically for stent related symptoms or post procedural pain [10]. Aside from the short-term repercussions of ureteroscopy with stent placement (such as ED visits), there are long-term issues related to pain or the treatment thereof. Recent evidence suggests that approximately 6% of opioid naïve patients who undergo ureteroscopy will become new persistent opioid users [11].

Alpha-blockers decrease ureteral stent discomfort when compared to placebo [12, 13]. Anti-muscarinic medications have also been shown to be helpful with stent related discomfort independently, or in addition to alpha blockade [14], though the evidence is mixed [15]. A recent systematic review failed to find any studies of other medications for stent related discomfort that met inclusion criteria [16]. Subsequently, a well-designed study demonstrated the utility of mirabegron for indwelling stent symptoms [17].

Recent guidelines recommend the use of multimodal treatment strategies in the management of postoperative pain [18]. In several contexts, gabapentin or pregabalin have been shown to be a beneficial part of such a strategy. For example, in percutaneous nephrolithotomy, a randomized, placebo-controlled, double-blind study demonstrated that a single dose of 600mg of oral gabapentin 1 hour before surgery significantly decreased catheter-related bladder discomfort, number of patients requiring opioid pain relief, and amount of opioid pain relief when used [19]. Similarly, outside urology, several well-designed trials demonstrate the positive effects of perioperative pregabalin or gabapentin in the elective, outpatient surgery setting [20-22]. Several reviews and meta-analyses have also supported the use of perioperative gabapentin or pregabalin in various settings [23-26]. The principal side effects of pregabalin are temporary cognition/coordination changes, with a very low risk of serious side effects [27]. No well-constructed studies to date have examined the perioperative use of gabapentinoids in post-ureteroscopy ureteral stent related symptoms.

In preparation for this work, we performed a pilot study looking at perioperative pregabalin use in ureteroscopy at our institution. We obtained IRB approval for a prospective feasibility study. We enrolled 10 patients undergoing ureteroscopy with stent placement at our institution. They all received 300mg pregabalin before surgery, along with a standardized regimen of post-operative and discharge medications. Patient centered outcomes were measured. Despite pre-operative counseling about pain control and stent discomfort, 20% expected to need opioid pain control. The only adverse effect reported more than once was dry mouth. All patients went home on the day of surgery, as is typical. No patient was prescribed opioid at discharge. One patient went to the emergency room in the first 30 post-operative days for a procedural pain related reason. Interestingly, it was actually immediately after stent removal. This patient was prescribed 90 oral morphine equivalents of tramadol. This rate of return is in line with contemporary reports [9].

We learned a great deal from this pilot study. First, we saw that it was feasible to enroll patients at a relatively high rate. We approached 12 eligible patients to enroll 10. A surprisingly high number (approximately 1/3) of patients undergoing eligible procedures were not eligible for enrollment, typically due to chronic kidney disease or chronic opioid use. We were successfully able to administer the study medication and track outcomes. The number of surveys were quite burdensome – to participants, nurses, and study staff. Insurance companies regularly required prior authorization for the recommended discharge medications (but would approve relatively similar medications). We have modified the design of this study in several ways due to the lessons learned in the pilot study.

CRITERIA FOR SUBJECT ELIGIBILITY

Subject Population

Undergoing elective ureteroscopy with stent placement at University of Missouri Hospital and affiliated facilities

Subject Inclusion

- Age $\geq$ 18 years
- Undergoing ureteroscopy with plan for stent placement

Subject Exclusion

- Renal insufficiency (eGFR < 50 mL/minute/1.73 m^2)
- Ureteral stent in place >30 days
- Chronic opioid use
- History of opioid abuse

- Chronic gabapentinoid use
- History of gabapentinoid abuse
- Plan for inpatient hospitalization either leading up to or after treatment
- Pregnancy
- Inability of the patient to consent for themselves in English
- Allergy to gabapentinoid
- Liver failure or hepatic dysfunction
- No email address that is regularly checked

OVERVIEW OF STUDY DESIGNATION

Design

This is a randomized, controlled clinical trial on the use of perioperative pregabalin in order to decrease ureteral stent related symptoms and decrease opioid usage after ureteroscopy with stent placement. Patients undergoing ureteroscopy with stent placement will receive a single dose of 300 mg pregabalin PO or an identical appearing placebo in the preoperative area.

Pre-op standardized care

After obtaining electronic written informed consent, patients will be enrolled.

Subsequently, all patients will be given a single dose of pregabalin 300 mg PO or an identical appearing placebo with a sip of water approximately one hour before surgery. This will be administered per standard intuitional practice. It will not be recorded in the regular medical chart of the patient.

Post-op standardized care

Perioperative care, surgery, and anesthesia for all subjects will be per standard hospital protocol.

To qualify for discharge from the PACU, per standard protocol, all patients will have had to have ambulated, voided, tolerated PO intake, and have pain subjectively adequately controlled.

THERAPEUTIC AND DIAGNOSTIC AGENTS

Pregabalin is an oral agent approved for use in fibromyalgia and neuropathic pain. A single dose of compounded 300mg PO will be given to all patients.

A standard inactive placebo will be used.

The medications will be compounded so as to have identical appearance. This will be performed by the investigational pharmacy at the University of Missouri.

RECRUITMENT PLAN

Patients will be recruited from the Division of Urology, Department of Surgery. The study will be introduced to every eligible patient scheduled for ureteroscopy with stent placement by the participating consenting physicians from the Department of Surgery-Urology Division and an electronic consent obtained prior to surgery by the consenting research personnel. Candidate subjects will be provided time to consider the study, to read the informed consent document at their convenience, and discuss the study with family and others, as desired. It will be clearly indicated that non-enrollment in the study will not negatively affect the patient's care.

PRETREATMENT EVALUATION

This study does not require any additional pretreatment evaluations other than those which are part of current clinical care standards for a patient undergoing ureteroscopy with stent placement at University of Missouri. Preoperative evaluations typically include the following:

- Routine history and physical examination to include documentation of any comorbidities, medications (including complementary and alternative medications), family history, social history (alcohol and tobacco usage), height, body weight
- Past medical history including previous treatment for addiction

- Past surgical history including other uses of stents in the patient's lifetime
- Evaluation of renal function
- Any woman of child bearing age who believes she may be pregnant receives a pregnancy test

SURGICAL PLAN

The technique of surgery will have been determined to be ureteroscopy with stent placement based on the discretion of the surgeon and patient. None of the techniques utilized in the study are considered experimental and all are considered standard therapeutic options for patients with indications for this procedure. Typical indications include nephroureterolithiasis and evaluation for malignancy.

The operating team will consist of surgeons at University of Missouri Department of Surgery-Urology Division. The procedures are performed under standardized general anesthesia with standard intraoperative vital sign monitoring.

EVALUATION DURING TREATMENT/INTERVENTION

Not part of usual care

This protocol requires several evaluations outside those typically used. These are all questionnaires.

Timing	Questionnaire	Respondent
Before day of surgery OR on day of surgery	Screening questionnaire	Study staff
	Baseline questionnaire and demographic information	Patient
	E-consent	Patient
	Preop Watson clock drawing test and visual analog scale of pain	Patient
Day of surgery	PACU	Study staff
	Watson clock drawing test and visual analog scale of pain $	Patient
3 days post op	Early patient questionnaire	Patient
7 days post op	Early patient questionnaire	Patient
30 days post op	30 days post op chart review	Study staff
	Early patient questionnaire $	Patient
90 days post op	Late patient questionnaire	Patient
6 months post op	Late patient questionnaire	Patient
1-year post op	Late patient questionnaire	Patient
	1-year post op chart review	Study staff
Untimed	Unanticipated contact	Study staff/Treatment staff
	Evaluation of trial	Patient

$ indicates questionnaires for which compensation will be provided. Please see details of compensation.

Usual care

Routine evaluation and management for those undergoing ureteroscopy with stent placement include:
ASA classification, assigned by the anesthesiologist
Deep venous thrombosis prophylaxis per standardized pathway
Estimated blood loss
Use of intraoperative fluids (crystalloid, colloid, blood products)
PACU medication
Discharge medication
Follow up plan

TOXICITIES/SIDE EFFECTS
Various symptoms have been associated with the administration of pregabalin in the perioperative setting. The risk of serious adverse events in this use of pregabalin is low [27] and the potential benefits of this treatment may outweigh the risks. This will be recorded in the PACU questionnaire.

Surgical complications will be assessed prospectively and retrospectively and reviewed using the institutional standard for complications reporting for all surgical patients as followed by the Department of Surgery. Standardized graded complications and adverse effects at UM utilize the five-point modified Clavien-Dindo system. Grade I include complications requiring monitoring but no intervention; Grade II requires bedside or medical treatment; Grade III constitute adverse events requiring surgical or procedural intervention with return to normal functioning; Grade IV includes disabling, life-threatening complications with resulting functional loss and grade V is death of the patient. This is a modification of the Clavien-Dindo system for reporting complications with defined, categorized and classified events that will be segregated into time periods of ≤30 days, 31-90 days and > 90 days after surgery and includes medication complications following NCI CTCAE version 5 guidelines.

CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The intraoperative period is defined as the period from anesthesia induction to the extubation of the trachea. The surgical time is determined from the incision to the final skin closure.

The postoperative period is defined as the period from the extubation to various study endpoints.

Blood loss is defined as the estimate accounted from the suction device and absorptive sponges during the procedure, as described and agreed upon by the surgeon, anesthesiologist, circulating nurse, and surgical technician as covered by institutional guidelines.

The patient's pain will be evaluated with a visual analogue scale of pain [28]. This may either be done digitally or by paper [29].

Adverse events will be measured with an optional PACU questionnaire for nurses as well as by monitoring of unanticipated contact.

Neurological changes will be measured using the Watson[30] clock drawing test.

Satisfaction will be evaluated via questionnaires at subsequent time points.

Need for opioid pain medication will be carefully tracked via patient questionnaire, chart review, and review of any available prescription database.

CRITERIA FOR REMOVAL FROM STUDY
Patients will be withdrawn from the study if they express a desire to do so or if it is determined to be in the patient's best interest to do so.

BIOSTATISTICS
Sample Size
The study will be powered with an 80% probability to detect a 10% difference in the primary outcomes. It will also assume a loss to follow up rate of 50%. This will require approximately 200 total subjects with a planned 1:1 placebo to active treatment enrollment ratio. We estimate at least 500 eligible procedures are conducted each year at our institution. Accounting for excluded patients and those who do not wish to participate, we estimate that full enrollment should be attainable within one year.

Analysis
A formal statistical analysis plan, crafted by the study team in partnership with the statistical consultants, will be finalized prior to data analysis.

The primary outcome will be the score on the visual analog scale of pain in the PACU.
Secondary outcomes reported will be the amount of opioid prescribed (in oral morphine equivalents) in the first thirty post operative days. Also reported will be the proportion of patients requiring narcotic pain medication, a composite of unplanned healthcare interactions within the first 30 post-operative days, PACU length of stay, nausea/vomiting, changes in cognition or coordination, and a composite of serious adverse events (ICU admission or death) within the 30 post-operative days.

Analyses will be performed in R. For the primary outcome, student's t-test will be used to compare the amount of opioid prescribed. For the secondary outcomes, either chi-squared or student's t-test will be performed to test for differences between those who received perioperative pregabalin and those who received placebo. For the secondary outcomes, multiple testing will be corrected using the Benjamini-Hochberg method [31].

RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

Research Participant Registration
We will confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

We will obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

Participant randomization
Randomization will be undertaken using the randomization module available in REDCap. Patients will be randomized to either "Group A" or "Group B". Medications will be distributed via the investigational pharmacy according to patient allotment. No one outside the investigational pharmacy will have knowledge of which group receives active medication.

DATA MANAGEMENT ISSUES

The research team will be responsible for project compliance, data collection, abstraction and entry, data reporting, IRB correspondence, problem resolution and prioritization and coordination of the protocol study team activities. The data collected for this study will be entered into a secure departmental server or will be stored online in the university approved resource, REDCap [32]. Source documentation and regulatory binders will be stored in a locked filing cabinet within a locked department office space. These sites are exclusively used for research documents and only members of the research team will have access to files for this study.

Quality Assurance
Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations will be monitored throughout the study period. Potential problems will be brought to the attention of the study team for discussion and action.

Data and Safety Monitoring
The MU Health Care Data and Safety Monitoring Plans can be found online.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response and staff education on clinical research QA) and departmental procedures for quality control, plus institutional committees that are responsible for monitoring the activities of the clinical trials program.

PROTECTION OF HUMAN SUBJECTS

Benefits and Risks
The experimental intervention (perioperative pregabalin administration) is currently used at University of Missouri Hospital through the ERAS protocol. Numerous studies have shown significant patient benefits in all fields, including Urology. Several reviews have demonstrated the efficacy and safety of perioperative

gabapentinoid administration. The principal side effects of pregabalin are temporary cognition/coordination changes, with a very low risk of serious side effects. Therefore, we do not believe that the therapeutic aspects of this trial pose any serious risk different from patients undergoing ureteroscopy with stent placement under standard procedures.

Toxicities and side effects
Adverse outcomes are not anticipated with the regimen of pregabalin used in this study. Patients are closely monitored during the perioperative period and any serious events will be immediately brought to the attention of the study staff. All potential side effects will be recorded in questionnaires.

Alternatives / Therapeutic options
The alternative to participation in the trial would be to undergo ureteroscopy with stent placement according to the surgeon's standard practice and not to participate in the study. The patient may or may not receive pregabalin in this case. No other aspect of patient care would differ.

Financial Costs and Burdens
The cost of study drug and study drug administration will be covered by the study and will not be billed to the patients.

Patient incentives
The patients will be offered the following compensation:

Timing	Amount	Requirement
Day of surgery	$5.00	Completion of day of surgery clock drawing test and visual analog scale
30 days post-op	$5.00	Completion of early patient questionnaire

We may extend this to later time points pending future funding.

Monies will be supplied to patients in the form of e-gift certificates.

Privacy and Confidentiality
We will keep the study records confidential. No identifiers will be used in any reports or publications resulting from the study.

Volunteering Nature of the Study
Participation is entirely voluntary. All aspects of patient's care and monitoring will be unaffected by whether the patient chooses to consent for the study.

Serious Adverse Event (SAE) Reporting
Any SAE will be reported to the IRB as soon as possible, but no later than 5 calendar days. The reporting procedure will be followed as outlined in the University of Missouri protocol found in the "Core Standard Operating Procedure for Event Reporting.".

INFORMED CONSENT PROCEDURES
Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. This may be performed by phone. Participants will also be informed that they are free to withdraw at any time. All participants will submit an electronically signed consent form. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB

Informed consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant will sign the electronic consent form. The participant will receive a copy of the informed consent form. A member of the study staff will also sign the electronic consent form.

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APPENDICES

Appendix 1 – REDCap instruments

See instruments_v1.0.pdf

Appendix 2 – Watson clock drawing form

See Watson_v1.1.docx

Appendix 3 – Instructions for Watson clock drawing test

See Watson_instructions_v1.0.pdf

Appendix 4 – Visual analog scale

See VAS_v1.1.docx

Appendix 5 – Post-op study specific instruction

See post-op_instructions_v1.0.pdf

Appendix 6 – Written consent and HIPAA authorization

See consent_and_hipaa_v1.3.doc

Appendix 7 – E-consent

See econsent_v1.0.pdf