PROTOCOL TITLE:
Effect of Preoperative Gabapentin on Postoperative Pain Associated with Ureteroscopy and Stents Insertion: a Double Blind, Randomized, Placebo Controlled Trial

PRINCIPAL INVESTIGATOR:
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OBJECTIVES:

The study's objective is to determine the efficacy of preoperative gabapentin in relieving postoperative pain, reducing opioid use, and improving quality of recovery in subjects undergoing urologic surgery.

We hypothesize that subjects receiving gabapentin will have lower pain scores, less opioid consumption, and better quality of recovery as compared to subjects who are given a placebo.

BACKGROUND:

Ureteroscopy is a preferred technique to treat small to moderate sized stones located on the urinary tract. Stent placement is commonly performed at the end of the procedure to maintain urine flow from the kidney. Following ureteroscopy and stent placement, patients often experience a variety of symptoms, including abdominal or flank pain, dysuria, urinary frequency, urgency or incontinence. Ureteral stent-related pain has a high prevalence, with one study suggesting that over 80% of the patients experienced such pain, which interferes with daily activities and impacts quality of life. [1]

Ureteral stent-related pain is multifactorial, poorly defined in the literature, and its pathophysiology remains largely unknown. Smooth muscle spasm, bladder mucosa irritation, inflammation and urine reflux are some of the hypothesized causes. Several pharmacologic treatments for ureteral stent related pain have been studied, including alpha- blockers, anticholinergics, nonsteroidal anti-inflammatory agents and drug eluting stents. [2]

Gabapentin is commonly accepted as part of multimodal pain management regimen after surgical procedures.[3] There is evidence that pretreatment with gabapentin is effective in preventing the urinary catheter-related bladder discomfort after urological procedures. In a 2007 study, Agarwal et al. showed that gabapentin administered before surgery reduced the incidence of catheter related bladder discomfort by 50% in the treatment group while pain was decreased by only 20% in the placebo control group. No difference in side effects between treatment groups was observed.[4] In another study of catheter related bladder discomfort, Bala et al. showed that preoperative administration of 1200 mg of gabapentin was more effective than 600 mg, and no significant side effects were observed in either group.[5]

To date, we are aware of no studies investigating ureteral stent related pain control with the use of preoperative gabapentin.

In our institution, ureteral stent related pain is mostly treated with opioid medication. We hypothesize that patients undergoing elective ureteroscopy and stent placement who received preoperative gabapentin will experience decreased pain, will have lower opioid consumption, and improved quality of recovery as compared to the placebo control group.

References:

1. Joshi HB, Stainthorpe A, MacDonagh RP, Keeley FX Jr, Timoney AG, Barry MJ. Indwelling ureteral stents: evaluation of symptoms, quality of life and utility. J Urol. 2003;169(3):1065-9.
2. Koprowski C, Kim C, Modi PK, Elsamra SE. Ureteral Stent-Associated Pain: A Review. J Endourol. 2016;30(7):744-53.
3. Schmidt PC, Ruchelli G, Mackey SC, Carroll IR. Perioperative gabapentinoids: choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology 2013;119(5):1215-21.
4. Agarwal A, Dhiraaj S, Pawar S, Kapoor R, Gupta D, Singh PK. An evaluation of the efficacy of gabapentin for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. AnesthAnalg. 2007;105(5):1454-7.
5. Bala I, Bharti N, Chaubey VK, Mandal AK. Efficacy of gabapentin for prevention of postoperative catheter-related bladder discomfort in patients undergoing transurethral resection of bladder tumor. Urology 2012;79(4):853-7.

INCLUSION AND EXCLUSION CRITERIA:

Patients with nephrolithiasis who will undergo elective ureteroscopy and ureteral stent placement will be screened preoperatively for study eligibility by study research personnel during or after their visit to the Urology clinic.

Inclusion Criteria

Age 18 years to 75 years
Patients with obstructive kidney stones undergoing elective ureteroscopy or cystoscopy with Ureteral stent placement

Exclusion Criteria

Age less than 18 or more than 75 years
Acetaminophen allergy
Gabapentin allergy
Hydromorphone allergy
Chronic use of gabapentin
History of chronic pain (Pain for > than 3 months)
Chronic renal insufficiency (Creatinine > 1.3)
Seizure disorder
Psychiatric disorders (medically treated)
Chronic use of anticonvulsants, antidepressants, antipsychotics (use > 3 months)
Antacids ingested within 2 hours prior to surgery
History of gastric or duodenal ulcer
Pregnant or lactating
Inability to communicate in English
Lactose allergy

Adults unable to consent N/A
Individuals who are not yet adults (infants, children, teenagers) N/A
Pregnant women N/A
Prisoners N/A

STUDY-WIDE NUMBER OF PARTICIPANTS: N/A

STUDY-WIDE RECRUITMENT METHODS: N/A

MULTI-SITE RESEARCH: N/A

STUDY TIMELINES:
Each enrolled subject will receive an e-mail from Northwestern University REDcap or a follow up telephone call 24 and 48 hours after surgery, and again approximately one week after surgery during a follow up visit in the Urology clinic.

Approximately five to eight elective ureteral stents are placed per week in Feinberg Urology operating rooms. If we are able to recruit ten to twelve patients per month, the anticipated duration for enrollment would be five to six months.

STUDY ENDPOINTS:
Primary endpoints:
48 hours opioid consumption

Secondary endpoints:
24 hours opioid consumption
24 & 48 hour Pain Burden
Gabapentin related side effects (sedation, dizziness, headache) (Likert Scale= Mild, Moderate, or Severe)
Evaluate urinary symptoms using the International Prostate Symptom Score (IPSS)
Evaluate quality of recovery using the Quality of Recovery 40 (QoR 40) questionnaire

PROCEDURES INVOLVED:
Approximately one hour prior to induction of anesthesia in preoperative holding area all enrolled subjects will receive PO Acetaminophen 650 mg, the Gabapentin group will receive PO Gabapentin 1200 mg, while the Control group will receive PO Placebo, with a small amount of water.

Upon arrival in the operating room, standard ASA monitors will be applied and the subjects will receive standard general anesthesia.

After extubation all patients will be transported to the PACU on 2-liter oxygen by nasal cannula, which will be weaned off in the PACU.

The postoperative analgesics during Phase I of recovery in PACU will consist of IV Hydromorphone 0.2-0.4 mg prn pain to maintain adequate pain control (NPRS<4). During Phase II of recovery patients will receive PO Hydromorphone 2mg tablets every 4-6 hours as needed for pain (NPRS ≥ 4) and acetaminophen 650mg PO every 6 hours

The following data will be collected every hour during phase I and phase II recovery:
- pain (NPRS)
- sedation (Ramsey sedation scale)
- dizziness (1- mild, 2- moderate, 3- severe)
- headache (Yes/No) If yes: NPRS score HA
- respiratory depression (hypoventilation/ apnea: RR < 10 bpm., desaturation: (SpO2 < 90%)
- Sedated but still in pain (Yes/No)
- PONV (Yes/No)
- PONV receiving antiemetic treatment
- *time to first opioid administration (IV hydromorphone)*
- *total amount of IV hydromorphone in PACU Phase I*
- *total amount of oral analgesic (hydromorphone) in PACU Phase II*
- *time to meet discharge criteria from PACU Phase I*
- *time to meet discharge criteria from Phase II*

Study research personnel will contact participants by Northwestern University secure e-mail invitation to REDcap or phone or in the hospital at 24 hours and 48 hours postoperative and at approximately one week in the Urology clinic. The study research personnel will ask questions regarding pain (NPRS) and analgesic consumption. The IPSS and QOR-40 questionnaires will be administered and data will be recorded.

DATA AND SPECIMEN BANKING: N/A

DATA AND SPECIMEN MANAGEMENT:
The primary outcome will be opioid consumption for the first 48 hours following surgery. Based on the study of Lingeman et al. (J Urology 2009; 181:2581-7), we estimate 48 hr opioid consumption to be 35 ± 15 mg IV morphine milligram equivalents (MME). Assuming a 30% reduction in opioid consumption in the gabapentin group, a sample size of 32 per group will achieve 80% power to show a difference in mean MME when there is a difference of -9 MME between the null hypothesis mean difference of 0.0 and the actual mean difference of 11 at the 0.05 significance level (alpha) using a two-sided Mann-Whitney-Wilcoxon Test. Thirty-five subjects will be recruited to each group to account for missing data and drop outs.

The primary outcome will be compared between the gabapentin and control group using the Mann-Whitney U test. Median differences and 95% confidence intervals will be determined using a bootstrapping method. Secondary outcomes will be compared using the Mann-Whitney test for continuous data and a chi-squared statistic. A $p<0.05$ will be required to reject the null hypothesis.

The data will be collected by the study research personnel or by e-mail invitation via REDcap. Subject data will be stored in the Northwestern University REDcap data collection system accessible only by using a secured departmental computer at Northwestern University Department of Anesthesiology office located in Arkes Pavilion, 10^{th} floor, 676 N. St. Clair, Chicago IL 60611.

Data are backed up every night using Northwestern University Department of Anesthesiology servers which are stored on the 5th floor of Arkes Pavilion and only accessible by the departmental IT administrator using key card and hard key as well as passwords.

Completed paper data collection forms will be stored in locked cabinets in the office of the principal investigator on the 10th floor Arkes Pavilion, Department of Anesthesiology. Only study team members will have access to review the data.

Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database. This will be kept in a dedicated Department of Anesthesiology password-protected computer in a locked office located on the 10 floor of Arkes Pavilion, Department of Anesthesiology office.

Strict measures will be in place to ensure that no loss of confidentiality occurs. Only study team members will have access to the data. The principal investigator will be oversee the handling and management of the data.

Data both electronic and paper will be destroyed 5 years after manuscript preparation using current department protocol and current vendor.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

A data monitoring committee will consist of the Department of Anesthesiology Director of Research, a statistician, and a faculty member from the Urology department. Safety and adverse event data will be collected when completing the data collection form and reviewing the side effect profile of the study drug. This information will be reviewed by research study personnel and the data monitoring committee every 15 subjects, or if one of the study subjects experiences a rapid response team intervention and review. Data will be compared between groups using the chi^2 statistic or the Fisher's exact test. A $p<0.05$ will be required to reject the null hypothesis.

WITHDRAWAL OF PARTICIPANTS:
Participants may be removed from the study at any point if the PI has determined that it is in the best interest of the subject, and the PI will discuss the reasons with the subject. All participants have the choice to remove themselves from the study, at any point during the study, without consequence. Data collected up to that point will be included in the data analysis.

RISKS TO PARTICIPANTS:
Gabapentin is an FDA approved drug. There is evidence that gabapentin can improve postoperative pain control after different type of surgeries, including urologic procedures. The risks associated with a single dose of gabapentin are minimal. It is known that administration of gabapentin has sedation effects and very rarely can depress breathing; therefore, the study participants will be closely monitored in both phases of recovery for potential side effects.

Risks of study drug (Gabapentin):
Frequent: asthenia (loss of muscle strength), malaise, face edema; hypertension, anorexia, flatulence, gingivitis, purpura most often described as bruises resulting from physical trauma, arthralgia, vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility, pneumonia, abnormal vision.

Infrequent: allergy, generalized edema, weight decrease, chill, hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, migraine, murmur, glossitis, gum hemorrhage, thirst, stomatitis, increased salivation, gastroenteritis, hemorrhoids, bloody stools, fecal incontinence, hepatomegaly, anemia, thrombocytopenia, lymphadenopathy; tendinitis, arthritis, joint stiffness, joint swelling, positive Romberg test, CNS tumors, syncope, dreaming abnormal, aphasia, hypesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, psychosis, epistaxis, dyspnea, apnea; alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cyst, herpes simplex, hematuria, dysuria, urination frequency, cystitis, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, unable to climax, ejaculation abnormal; cataract, conjunctivitis, eyes dry, eye pain, visual field defect, photophobia, bilateral or unilateral ptosis, eye hemorrhage, hordeolum, hearing loss, earache, tinnitus, inner ear infection, otitis, taste loss, unusual taste, eye twitching, ear fullness.

Rare: strange feelings, lassitude, alcohol intolerance, hangover effect, atrial fibrillation, heart failure, thrombophlebitis, deep thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystoles, bradycardia, premature atrial contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, pericarditis, dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perlèche,

salivary gland enlarged, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, esophageal spasm, hyperthyroid, hypothyroid, goiter, hypoestrogen, ovarian failure, epididymitis, swollen testicle, cushingoid appearance, WBC count increased, lymphocytosis, non-Hodgkin's lymphoma, bleeding time increased, costochondritis, osteoporosis, bursitis, contracture, choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, lung edema. herpes zoster, skin discolor, skin papules, photosensitive reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodules, subcutaneous nodule, melanosis, skin necrosis, local swelling, kidney pain, leukorrhea, pruritus genital, renal stone, acute renal failure, anuria, glycosuria, nephrosis, nocturia, pyuria, urination urgency, vaginal pain, breast pain, testicle pain, eye itching, abnormal accommodation, perforated ear drum, sensitivity to noise, eye focusing problem, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative eye changes, blindness, retinal degeneration, miosis, chorioretinitis, strabismus, eustachian tube dysfunction, labyrinthitis, otitis externa, odd smell.

Risk of Placebo:
None

Other risks:
Completing the surveys may make subject feel anxious. There is the potential for loss of confidentiality even though there are strict measures in place to prevent such an occurrence.

POTENTIAL BENEFITS TO PARTICIPANTS:

The potential benefit from participating in the study and receiving the study drug would be improved pain control and decreased amount of pain medication, therefore fewer side effects and improved quality of recovery.

VULNERABLE POPULATIONS: N/A

COMMUNITY-BASED PARTICIPATORY RESEARCH: N/A

SHARING OF RESULTS WITH PARTICIPANTS:

At study completion, participants may be notified of their treatment group assignment at their request.

SETTING:
Participants will be identified in the Emergency Department (ED) or, in the hospital the day before their planned surgical procedure or during their standard of care visit to the Northwestern Memorial Hospital Urology Clinic (Galter Pavilion, 20th Floor, Suite #150). The patient's EMR will be reviewed by a study team member to determine eligibility.

Eligible patients will be approached in clinic by a member of the study team who will provide an overview of the study. Patients may also be contacted over the phone after their visit by their physician who is also an authorized member of the study team (Dr. Robert Nadler). Patients will have the option of taking the consent form home, or have the consent form emailed or mailed to them using the information in their EMR, for further consideration of participation. This information will not be stored.
The study drug will be administered before surgery in the preoperative area at Northwestern Memorial Hospital (Galter Pavilion, 5th Floor). Intraoperative and postoperative care will take place in the Urology operating rooms, phase I and phase II recovery rooms.

For outpatients, the follow up will be by e-mail (REDcap), phone, and for inpatients, they will be followed up in person on the admission floor, at 24 and 48 hours. The one week follow up will take place in the Urology clinic.

RESOURCES AVAILABLE:
The study research personnel will be fully informed about the research protocol. Copies of the protocol will be available for review in the Urology clinic, Anesthesiology Ready Room, and the urology operating rooms in Feinberg pavilion.

After enrollment in the Urology clinic, the study will be conducted in the preoperative area (Galter Pavilion, 5th floor) and Feinberg Urology ORs and recovery rooms. Study research personnel will collect intraoperative and postoperative data. For outpatients, the follow up will be by phone, and for inpatients, they will be followed up in person on the admission floor, at 24 and 48 hours. The one week follow up will take place in the Urology clinic.

PRIOR APPROVALS:
The Department of Anesthesiology Research Committee

RECRUITMENT METHODS:
Participants with a diagnosis of obstructive nephrolithiasis and scheduled to undergo elective ureteroscopy/cystoscopy and ureteral stent placement will be identified in the Emergency Department (ED) or, in the hospital the day before their planned surgical procedure or during their standard of care visit to the Northwestern Memorial Hospital Urology Clinic (Galter Pavilion, 20th Floor, Suite #150). The patient's EMR will be reviewed by a study team member to determine eligibility.

Eligible patients will be approached in clinic by a member of the study team who will provide an overview of the study. Patients may also be contacted over the phone after their visit by their physician who is also an authorized member of the study team (Dr. Robert Nadler). Patients will be given as much time as they need to ask questions and consider their participation. Patients will have the option of taking the consent form home, or have the consent form emailed or mailed to them using the information in their EMR, for further consideration of participation. This information will not be stored.

Once the patient decides to participate, they will meet at NMH with a member of the study team who will answer any further questions and obtain informed consent. Patients will receive a copy of the signed informed consent form for their records.

NUMBER OF LOCAL PARTICIPANTS:
We will seek to enroll a total of 70 patients, 35 patients in each treatment group with 1:1 randomization.

CONFIDENTIALITY:
Data will be stored in a Northwestern University Department of Anesthesiology dedicated computers which are only accessible to the study research personnel. The computers are password protected and are located on the 10th floor Arkes Pavilion Department of Anesthesiology administrative office. The computers are backed up every night to the Department of Anesthesiology server located on the 5th floor Arkes pavilion. A key card and key are required and is only accessible by the Department of Anesthesiology IT administrator. The server is remotely backed up nightly.

Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database. Data access will be password protected and only available to study investigators.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
The subject will have multiple interactions with the study team. The first interaction will be to discuss and obtain written informed consent, then several times over the next week for brief periods for follow up purposes. These brief interactions will limit the amount of intrusion into the subject's surgical recovery.

The subject will be treated with respect and dignity by mandating that study research personnel introduce themselves and remind the subject about their participation in the study. The follow up will be completed by study research personnel who will remind the participant why this encounter is occurring.

The study research personnel are only allowed to view the data sheets and EMR for selected data within the parameters of the study, including to obtain medication use during recovery.

COMPENSATION FOR RESEARCH-RELATED INJURY: N/A

ECONOMIC BURDEN TOPARTICIPANTS:
There is no additional cost to participate in this study. All participants will be charged for standard care they receive including the cost of the analgesia that they would receive if they had not participated in this study. This cost will be billed to their insurance providers.

CONSENT PROCESS:
Eligible patients will be approached in the Emergency Department (ED) or, in the hospital the day before the planned surgical procedure or clinic by a member of the study team who will provide an overview of the study. Patients may also be contacted over the phone after their visit by their physician who is also an authorized member of the study team (Dr. Robert Nadler). They will be able to review the consent document and take as much time as they need to ask questions and consider their participation. Patients will have the option of taking the consent form home, or have the consent form emailed or mailed to them using the information in their EMR, for further consideration of participation.

If they agree to be a participant in the study they will sign the consent document. They will be consented ahead of their planned surgical procedure. The length of time is greater than 10 minutes discussing the consent document and the procedures involved.

Ample time will be allowed for patient to ask questions regarding the study and the consent document. The subject will also be informed that there is no conflict of interest between the PI and the protocol. The PI will not receive financial remuneration nor will the study participation affect the subject's financial charges for their care.

Waiver or Alteration of Consent Process: N/A

Participants who are not yet adults (infants, children, teenagers) N/A

Adults Unable to Consent: N/A

PROCESS TO DOCUMENT CONSENT IN WRITING:
Study team member will review the consent document with the subject and sign the consent document. The subject will then sign the consent document after reviewing the document. The checklist documenting informed consent will also be completed by the

study team member obtaining written informed. A copy of the consent document will be copied and given to the subject. Additional copies will be placed with the pharmacy and the subject's medical chart.

DRUGS OR DEVICES:

Gabapentin qualifies for FDA exemption for this protocol.

1. The drug is lawfully marketed in the United States.
2. The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
3. The research is not intended to support a significant change in the advertising for the product.
4. The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.5. The research is conducted in compliance with the marketing limitations described in 21 CFR

Pharmacy will have the randomization table & dispense the study drug or placebo. The study drug and placebo will be stored in the 5th floor surgical pharmacy of Feinberg Pavilion. The anesthesiologist, PACU and ASU nurses and study research personnel will be blinded to the study group. The Anesthesia research personnel will administer the study drug to the patient approximately1 hour before the surgery.