Research Study Protocol

Title: Randomized placebo control trial of perioperative gabapentin to reduce total analgesic requirements in patients undergoing radical cystectomy

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Background and Significance: Approximately 73,000 patients will be diagnosed with bladder cancer in the US in 2013. Of these, 30% will have muscle-invasive[1] for which surgical therapy via a radical cystectomy (RC) with urinary diversion is the standard of care. Despite advances in surgical and anesthetic techniques and improvement in post-operative care, RC remains extremely morbid with rates of complications, readmissions, and 90-day perioperative mortality approaching 50%, 30%, and 7% respectively.[2,3] Thus strategies to reduce RC patients' morbidity and suffering are needed.

One such potential strategy is to improve patients' post-operative pain management. Not only does post-operative pain contribute to patient suffering, pain (and lack of pain control) may also contribute to perioperative morbidity. For example, pain decreases patient ambulation following surgery, which in turn is associated with a number of post-operative complications, including thromboembolic events, for which the incidence (3.7%) in the RC population is the highest among surgical patients. [4] Additionally, the perception of pain [5] and excessive use of narcotic pain medications are major contributors to the development of prolonged post-operative ileus, which effects nearly 20% of RC patients [6] and is a major cause of prolonged hospitalization. Consequently, strategies aimed at improving pain control and reducing narcotic requirements could be beneficial in reducing both patient discomfort and the development of complications.

Recently, the use of perioperative gabapentin has been evaluated in a number of surgical populations as a strategy to improve patient pain control and reduce total analgesic requirements. [7] For example, a recent placebo controlled randomized trial demonstrated that 1,200 mg gabapentin given in the pre-operative suite prior to hysterectomy was associated with improved patient perception of pain on visual analog scale for 24 hours and an approximately 35% decrease in narcotic use over the first 24 hours post-operatively. [8] Similarly, in another study, patients receiving preoperative gabapentin prior to open cholecystectomy had an approximately 25% relative reduction in analgesic requirements, as well as significantly decreased postoperative pain and nausea/vomiting compared to those receiving placebo. [9] Based on these encouraging data, we propose a double blind placebo controlled randomized trial evaluating the use of perioperative gabapentin in patients undergoing RC.

Study Population: We will include 44 adult patients with a diagnosis of bladder cancer undergoing radical cystectomy with urinary diversion (ileal conduit ororthotopic neobladder, etc)

Study Design: The proposed study is a randomized double-blind placebo controlled trial studying the use of perioperative oral gabapentin (1,200 mg (4 X 300 mg caps) one hour before surgery plus 300 mg 3x's daily for 48 hours) as an adjunct pain medication in the RC population. Following IRB approval and with informed consent, we plan to recruit 44 patients undergoing RC at UWMC to achieve a power of 0.8 at α <0.05 in order to detect a 30% difference in analgesic requirement over 48 hrs. Patients will be randomized 1:1 into receiving gabapentin as outlined above or a placebo designed to look like 300 mg caps with the same dosing. Patients will be stratified by urinary diversion type. Study medications will be administered by nurses in the pre-operative suite and on the floor. The surgical and anesthesia/pain service team will be blinded to the group assignment. Following RC, all patients will receive our standard post-operative pain management regiment, including scheduled acetaminophen (every 6 hours) and ketorolac (every 8 hours) and morphine patient-controlled analgesia, and will be transitioned to oral narcotics as clinically indicated, generally at 48 hours post-op. Patients' postoperative pain will be assessed on a verbally administered numerical pain scale (NPS) (0-10 scale) at time 0 (arrival in the recovery room) and at 1 ± 0.25, 4 ± 0.25, 12 ± 0.25, 24 ± 0.25 and 48 ± 0.25 hours post-RC by the patients' nurse and prospectively recorded in the patients' chart and abstracted by the study coordinator. A NPS was chosen because of their ease of use compared to visual analog scales, particularly for elderly patients.[10] Each patient's total analgesic use for the first 48 hours post-op will be recorded, as will time to first flatus and bowel movement, LOS, and adverse events.

Study Procedure Chart:

	Pre-Enrollment	Pre-op	Day of Surgery	POD1	POD2
Recruitment	X				
Informed Consent	X				
Randomization		X			
Surgery			X		
Medications					
Study Drug or Placebo			Once	3x's Daily	3x's Daily
Tylenol (acetaminophen)				4x's Daily	4x's Daily
Toradol (ketorolac)				3x's Daily	3x's Daily
Morphine (patient controlled analgesia)				X*	X*
Pain Assessment					
Numeric Pain Scale (NPS)			X	X	X**

POD = post-operative day

* will be adjusted per usual clinical care to meet patient pain requirements

** Pain will continue to be assessed following the 48 hour time period per usual clinical care

Sample Size: Based on a power calculation, to achieve a power of 0.8 at $\alpha < 0.05$ in order to detect a 30% difference in 48 hour with mean morphine equivalents, with population mean of 100 ± 50 mg we plan to enroll a total of 44 patients undergoing RC for a diagnosis of bladder cancer, including 22 patients in each arm.

Study Duration: Based on an annual RC volume of 100 cases/year, we anticipate approximately 7-10 patients will be eligible for our study per month. Assuming a 50% acceptance rate for enrollment in a clinical trial, we believe that accrual will take approximately 12 months.

Objectives:

Primary Objectives:

1) To assess if perioperative gabapentin will decrease post-operative analgesic requirements within the first 48 hours after RC in patients undergoing RC as measured morphine equivalents

Secondary Objectives:

1) To assess patient self-assessment of postoperative pain on NPS at 24 and 48 hours
2) To assess time to return of bowel function (ROBF)
3) To assess length of stay (LOS) following RC

Recruitment: Recruitment will be done for patients who are consenting to undergo a radical cystectomy with urinary diversion for a diagnosis of bladder cancer. Prior to initiation of recruitment, all clinic staff will undergo a briefing by Dr. Wright and the study team describing the study, its goals, and methodology. At the first clinic visit in which radical cystectomy is discussed with the patients for their diagnosis of bladder cancer, possible participants will be screened for enrollment in the study. Possible participants will then for their diagnosis of bladder cancer, the patient will have the study described to them. If the patient expresses interest, informed consent will be obtained. Participants will be provided with a copy of the study design, IRB approval and Study Procedure Chart. Following informed consent, the patient will be scheduled for RC per routine care. Participants will be under no obligation to participate in the study and the decision whether or not to perform surgery will not be affected based on patient participation. All enrolled patients PHI will be stored in a locked office and all electronic PHI will be stored on password protected/encrypted computers and/or drives within the UW Department of Urology.

Inclusion/Exclusion Criteria:

Inclusion:

1) Age ≥ 18 years old
2) Diagnosis of bladder cancer
3) Anticipated radical cystectomy with ileal conduit or orthotopic neobladder

Exclusion:

1) Age less than 18 years, Age > 75 years
2) Presence of spinal cord injury including any form of paraplegia or quadriplegia
3) Allergy to gabapentin

4) Active alcohol dependence, defined as 2 or more positive questions on the CAGE alcoholism questionnaire[12]
5) Illicit drug use (excluding recreational marijuana)
6) Chronic kidney disease with glomerular filtration rate <30 ml/min
7) Pregnancy: All female patients <55 yo will be administered a urine pregnancy test prior to enrollment
8) Non-English speaking patients
9) Chronic gabapentin, or the similar drug pregabalin, use
10) Chronic narcotic use (daily or near daily use for >90 days)

Study Procedures:

After consent is obtained during the clinic visit, the participant will be scheduled for RC per standard procedure. Participants will then undergo randomization, stratified by patient sex to ensure equal randomization (50% chance of receiving gabapentin) for both male and female patients. A third party member not involved in the study design or write-up will place participant study arm randomization status within a sealed envelope. On the date of surgery, the sealed envelope will be opened by Investigational Drug Services and the appropriate study drug (gabapentin or placebo) will be assigned and dispensed to the participant as described.

Participants will be administered an oral dose of gabapentin (1,200 mg (4 X 300 mg caps) or an identical placebo (4 caps) one hour before surgery in the preoperative suite by the participants nurse. They will then undergo the planned procedure. Following RC, participants will be administered gabapentin 300 mg 3x's daily by mouth for 48 hours or an identical placebo by the acute care nurse. The surgical and anesthesia/pain service team will be blinded to the group assignment. Following RC, all patients will receive standard post-operative pain management, including acetaminophen, morphine patient-controlled analgesia per the acute pain service, toradol and will be transitioned to oral narcotics as clinically indicated. Patients' postoperative pain will be assessed on NPS (0-10 scale) at time 0 (arrival in the recovery room) and at 1 ± 0.25, 4 ± 0.25, 12 ± 0.25, 24 ± 0.25 and 48 ± 0.25 hours post-RC. Each patient's total analgesic use for the first 48 hours post-op will be recorded and converted to total morphine equivalents using the Agency Medical Director's Group of Washington morphine equivalents calculator (http://www.agencymeddirectors.wa.gov/opioiddosing.asp), as will time to first flatus and bowel movement, total LOS, and adverse events. Discharge from the hospital following RC will mark the end of each participant's participation in the study. Subsequent follow-up and care will be per routine care for RC.

Outcome Assessment: The primary endpoint will be patient total equivalent analgesic requirement (morphine equivalents) for the first 48 hours post-RC. Secondary endpoints will include patient self-assessed pain on NPS, the time to ROBF will be determined by time to first flatus and bowel movement and LOS following RC as calculated from the date of surgery to the date of discharge.

Statistical Analysis: Assessment of the primary outcome will be by total morphine-equivalents required over the first 48 hours after RC. The two study groups will be compared using the t-test with $p<0.05$ considered statistically significant. The secondary endpoints pain on NPS, time to

ROBF and LOS will be evaluated similarly. All outcomes will be analyzed in an intention to treat analysis. Regression analysis will be used to determine patient and clinical factors that predict response to gabapentin, with adjustment for age, sex, ethnicity, analgesic use at the time of RC, pathologic stage, estimated blood loss, and operative time. Data analysis will be performed using Stata 12.1. Based on a power calculation to achieve a power of 0.8 at $\alpha < 0.05$ in order to detect a 30% difference in analgesic requirement over 48 hrs we plan to recruit 40 patients undergoing RC at UWMC to.

Pharmaceutical Information:

Gabapentin is a potent analgesic and anticonvulsant that illicits effects through unclear mechanisims. From an analgesic standpoint, gabapentin prevents allodynia (pain-related behavior in response to normally innocuous stimulus), hyperalgesia (exaggerated response to painful stimuli), pain-related responses in several models of neuropathic pain, and decreases pain-related responses after peripheral inflammation. Currently gabapentin is FDA approved as an anticonvulsant and for post-herpetic neuralgia and is widely used clinically for management of neuropathic pain, other chronic pain sources, and increasingly as an adjunct therapy for perioperative pain.

The drug comes in many forms including 100 mg, 300 mg, 400 mg, 600 mg and 800 mg capsules or an oral solution. Main adverse effects are related to the principal active ingredient. Gabapentin may case dizziness, somnolence and other symptoms and signs of central nervous system depression. Additionally, gabapentin is included in an FDA warning of a possible association between anticonvulsant use and suicidal thoughts and behaviors. However, in a meta-analysis including greater than 131,000 patients gabapentin was use was not associated with a suicide attempts (3.48/1000 person years prior to gabapentin use vs. 3.45/1000 person years after gabapentin prescription).[13]

Contraindications to use include hypersensitivity to the drug or its ingredients.

We will be utilizing UWMC Investigational Drug Services to provide both gabapentin (300 mg capsules) and placebo in identical capsules. Medications will be dispensed through UWMC Investigational Drug Services.

Privacy and Confidentiality

Human subject's names will be kept on a password-protected database and will be linked with a study identification number for this study. All clinical data will be stored in a separate database using the study ID number without any patient identifiers. All data will be entered/stored on a password protected computer/drive. Written data will be stored in a locked office of the investigators and maintained for a maximum of three years after the completion of the study.

Risk/Benefit

Risk to Participants: The primary risk to participants during the study is adverse effects from the medication. Generally, however, gabapentin is well tolerated with the most common side effects

being dizziness and somnolence for which patients will be closely monitored. Since the medication will be given as part of the participants' otherwise routine post-operative care, we do not anticipate other changes to their post-operative care

Benefits: The study will provide level-1 evidence regarding the use of perioperative gabapentin in a patient population exposed to considerable perioperative pain and morbidity related to RC for management of bladder cancer. If efficacious, perioperative gabapentin could significantly reduce perioperative analgesic (narcotic) use while improving perioperative pain and convalescence in a high-risk patient population, thereby considerably improving their perioperative quality of life.

Data Safety Monitoring: An independent safety monitoring board will meet every 6 months to monitor for adverse events. Any unexpected severe adverse event (SAE) identified will be reported to the FDA within 7 days.

Severe Adverse Events: According to the FDA, SAE are defined as "Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect." Additionally, "Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." All patients will be monitored for AEs throughout their hospital stay. Any event determined to be a SAE by the data safety monitoring board will be reviewed and if determined to be unexpected will be reported to the FDA in accordance with (21 CFR 312.32(c)(1)(i)).

Publications/Presentations: Data produced from this study will be presented at academic meetings/forums and will be submitted for publication in pertinent scientific journals (ie., *Journal of Urology*)

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