

Gabapentin Regimens and Their Effects on Opioid Consumption

A randomized controlled trial

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Background and Significance

Gabapentin is a first-line therapy for treating neuropathic pain in adults, and is also well known as a treatment for epileptic seizures. Its exact mechanism of effect remains uncertain [1], but gabapentin has been found to reduce acute pain on its own [2–3], to limit cravings and symptoms of withdrawal in people addicted to substances [4–6], and to decrease nausea [7–8].

Perhaps gabapentin's greatest benefit is to decrease opioid use in patients as they recover from surgery. Patients who take gabapentin in conjunction with opioids after surgery, or even in the two-hour window beforehand [9–18], take fewer opioid medications and experience little to no side-effects during the recovery process [19–24].

We wanted to determine the best strategy of administering gabapentin in connection with our current approach to perioperative pain management. We wanted to balance gabapentin's obvious usefulness with its own side effects; gabapentin can cause drowsiness and unsteady bearing [11, 15–18] and poses its own small risk of addiction and abuse [24]. We therefore propose a two-armed trial to evaluate different adjunct gabapentin regimens given in the perioperative period, and to identify which manages patient pain most effectively and safely. In this evaluation, we will identify the quantity of patients' opioid consumption, the quality of their pain management, and the frequency and severity of any side effects they might experience.

Specific Aims

With this project, we intend to determine whether administering a regimen of gabapentin after surgery can reduce opioid consumption more effectively than the standard of care, which is a single preoperative dose of 600 mg, followed by a dose of 600 mg each morning during postoperative admission. The experimental regimen would add one week of standing gabapentin followed by a month of nightly doses. Furthermore, we would like to know more about gabapentin's potential to cause drowsiness in patients and whether it has any effect on their ability to sleep after surgery. Finally, we want to know how long patients remain on gabapentin after surgery.

Subject Selection

Inclusion Criteria:

- At least 18 years of age
- Receiving surgery for total knee replacement (TKR)
- Opioid naïve

- Agrees to use tracking diary to monitor opioid consumption

Exclusion Criteria:

- Over 75 years of age on the date of surgery
- If female, pregnant
- Has received investigational articles < 30 days prior to enrollment or is currently receiving investigational products or devices
- Chronic pain syndrome
- Taking chronic narcotics and/or taking more than 10 mg of codeine per day, any amount of Hydrocodone, over 200 mg of tramadol per day, or any other narcotics prescribed for moderate or severe pain
- Involved in pain clinics for chronic pain, or pain that is not related to the surgical site
- On long-term gabapentin regimen
- Taking Lyrica or Gralise
- Known history of depression or has been treated for depression with medication
- Has entertained suicidal thoughts and behaviors

Subject Enrollment

Patients who schedule total knee replacement (TKR) with Dr. Wolfgang Fitz at Brigham and Women's Faulkner Hospital and meet all eligibility criteria will be informed about the study during their preoperative appointment. Specific topics discussed will include an introduction to the patient-maintained diary to document narcotic medications, and the PI's use of gabapentin for his surgical patients. All patients will be offered the chance to discuss with both the RA and the Principal Investigator (PI) and ask questions.

Each qualifying patient will be sent a letter describing the study and asking the patient to consider participating. After a reasonable elapse of time, the RA will call the patient by phone and ask whether the patient agrees to participate. The patient's response to this request will be recorded in research records. During this phone call, the RA will confirm that the patient meets the inclusion criteria and does not meet any exclusion criterion. If, later in the study, a patient meets any one of the exclusion criteria, he or she will be removed from the study.

Patients' informed consent will be obtained by the research assistant(s) when they come to the hospital for pre-op testing. If this is somehow impossible, written informed consent may be obtained in preoperative holding before surgery. Upon giving consent, the patient will be randomly assigned to a treatment group using computer-generated randomization.

The study will have two treatment arms:

Patients in Group 1 will receive the standard of care as pertains to gabapentin. This consists of a single 600 mg dose of gabapentin administered to the patient approximately one to two hours before surgery, then a dose of 600 mg each morning during postoperative admission.

Patients in Group 2 will receive the above standard of care, plus an additional home regimen: they will take 300 mg of gabapentin every 8 hours for 1 week, then a single nightly dose of 300 mg for another month.

Patients in both groups will record the amount of pain medications they consume and answer enclosed VAS scales every day in a tracking diary.

Study Procedures

Every patient being discharged from the hospital will receive from the nursing staff verbal and written instructions — the latter of which will be either printed or in electronic form — about narcotic medications. The instructions will explain when to use opioid medications and how to taper off their consumption. Following discharge, patients will take gabapentin as directed by their discharge instructions, and in the process track their opioid consumption on their own in their diaries. They will also document their pain, nausea and satisfaction levels according to the visual analogue scale (VAS).

At the first post-operative appointment, approximately 9–10 days following surgery, patients' levels of opioid use will be verified and compared to the amount recorded in each diary; the actual number of tablets consumed will be compared with the documented amounts and with the prescriptions they received. Patients receiving a new prescription will also receive a matching diary for the total length of opioid treatment, including further directions on how to wean themselves off their opioid medications.

Our primary outcome measures will be the amount of patients' opioid consumption, calculated in total doses of morphine equivalent, and the total number of days the patients took opioids. Our secondary outcome measures will be VAS scores for surgical site pain (both at rest and during physical activity), nausea, sleep quality, and satisfaction with pain management — all of which are reported on a daily basis within the tracking diary. Tertiary outcome measures will be the number of patients who are taking gabapentin beyond the length of time prescribed by the study, measured at the second postoperative visit 2–3 months after surgery.

Additional data including length of stay, postoperative complications including infection and readmission, ED visits and routinely collected postoperative functional outcome measures (PROMS) will be recorded.

Biostatistical Analysis

We will be comparing the two arms of the trial to see whether there exists a statistically significant difference between them. Variables in which we are interested include total opioid consumption, the amount of days spent using opioids, and the amount of days spent taking gabapentin. We will also record the other outcome measures detailed in the previous section. When comparing the branches, all analyses will be run at a type I error rate of 5%.

The study will end once we have enrolled the requisite number of patients in the study and taken the diary-based data from them. According to previous literature on the opioid-sparing effects of gabapentin, experimental groups tend to consume anywhere between 20% and 50% fewer opioid medications than control groups, with the average approximately 35%, and standard deviation approximately half the mean [9, 22, 23, 25]. Powering the study to detect this approximate difference, the total number of patients will be 68, with 34 in each arm.

Risks and Discomforts

Members of both interventions are at the standard risk for TKR patients for long-lasting opioid dependence following surgery, which can be about 8%. Patients who attempt taper off their medications too quickly are at risk of experiencing acute post-operative pain. Patients in the intervention group, who will be administered gabapentin for a greater length of time, may be at greater risk for gabapentin dependence than members of the control group.

Potential Benefits

While we do not guarantee benefits to participation, it is possible that the members of our intervention group may taper off their narcotic medications more quickly and more successfully than those who receive our standard of care, thus lessening their risk of long-term dependence on the medications. This could result in increased health and satisfaction.

We hope that finding an optimal gabapentin regimen can help patients reduce their narcotic consumption after total knee replacements, which will reduce their risk of becoming dependent on narcotics for pain management. Results of the study thus may help improve medication regimens for future patients.

Monitoring and Quality Assurance

The principal investigator will take responsibility for regular reviews of the study's progress and any concerns regarding subject safety. Study progress including data completion and entry will be discussed at protocol meetings to be held as needed during the duration of the protocol activity. The principal investigator will report adverse events or other unanticipated problems to PHRC as described in the PHRC policy on Adverse Event Reporting and Unanticipated Problems Involving Risks to Subjects or Others.

Adverse events will be reported immediately to the PI and to the IRB in accordance with the IRB adverse event reporting guidelines.

The principal investigator is responsible for adherence to all IRB rules and guidelines. The research coordinator will be responsible for the accuracy and completeness of all forms, entries, and informed consent. As an added quality assurance measure, study staff will hold monthly meetings to ensure that adherence to protocol is maintained by all of the study staff as well as to

monitor the status and quality of the study. Subject data will be kept on a protocol-specific, password-protected, Partners Healthcare System-maintained computer that is kept in a locked office. PHS computers maintain the latest anti-virus software and firewall protections.

Patients will be identified only by an identification code, and not by their name, SSN, or hospital medical record number. Research staff will maintain a separate confidential enrollment log which matches identifying codes with the patients' names and addresses available only to IRB-approved study staff.

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number.

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