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# Perioperative gabapentin reduces 24 h opioid consumption and improves in-hospital rehabilitation but not post-discharge outcomes after total knee arthroplasty with peripheral nerve block

H. A. Clarke[1,2,4]*, J. Katz[1,4,5], C. J. L. McCartney[2,4], P. Stratford[6,7], D. Kennedy[6], M. J. Pagé[5], I. T. Awad[2,4], J. Gollish[3] and J. Kay[8]

[1] Department of Anaesthesia and Pain Management, Toronto General Hospital, Toronto, ON, Canada
[2] Department of Anaesthesia and [3] Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[4] Department of Anaesthesia, University of Toronto, Toronto, ON, Canada
[5] Department of Psychology, York University, Toronto, ON, Canada
[6] School of Rehabilitation Science, [7] Department of Clinical Epidemiology and Biostatistics and [8] Department of Anaesthesia, McMaster University, Hamilton, ON, Canada

* Corresponding author. E-mail: hance.clarke@utoronto.ca, hance.clarke@uhn.ca

## Editor's key points

- Gabapentin is known to improve postoperative pain scores and to reduce opioid consumption after surgery.
- The authors studied the effect of perioperative gabapentin on knee function after arthroplasty.
- They were unable to show an improvement in knee function or movement-evoked pain.
- Early analgesic consumption and knee range of motion (secondary outcomes) were improved.

**Background.** This study was designed to determine whether a 4 day perioperative regimen of gabapentin added to celecoxib improves in-hospital rehabilitation and physical function on postoperative day 4 and 6 weeks and 3 months after total knee arthroplasty (TKA).

**Methods.** After Research Ethics Board approval and informed consent, 212 patients were enrolled in a randomized, double-blinded, placebo-controlled study. Two hours before surgery, patients received celecoxib 400 mg p.o. and were randomly assigned to receive either gabapentin 600 mg or placebo p.o. Two hours later, patients received femoral, sciatic nerve blocks, and spinal anaesthesia. After operation, patients received gabapentin 200 mg or placebo three times per day (TID) for 4 days. All patients also received celecoxib 200 mg q12 h for 72 h and i.v. patient-controlled analgesia for 24 h. Pain and function were assessed at baseline, during hospitalization, on postoperative day 4 (POD4), and 6 weeks and 3 months after surgery.

**Results.** The gabapentin group used less morphine in the first 24 h after surgery [$G$=38.3 (29.5 mg), $P$=48.2 (29.4 mg)] ($P<0.0125$) and had increased knee range of motion compared with the placebo group in-hospital ($P<0.05$). There were no differences between groups in favour of the gabapentin group for pain or physical function on POD 4 [95% confidence interval (CI): pain: −1.4, 0.5; function: −6.3, 2.0], 6 weeks (95% CI: pain: 0.1, 1.9; function: −0.2, 6.5) or 3 months (95% CI: pain: −0.2, 1.7; function: −2.2, 4.3) after TKA.

**Conclusions.** In the context of celecoxib, spinal anaesthesia, femoral and sciatic nerve blocks, a dose of gabapentin 600 mg before operation followed by 4 days of gabapentin 200 mg TID decreased postoperative analgesic requirements and improved knee range of motion after TKA. Gabapentin provided no improvement in pain or physical function on POD4 and 6 weeks or 3 months after surgery.

**Keywords:** functional outcomes; gabapentin; multimodal analgesia; pain; patient-reported outcome measures; physiotherapy; total knee arthroplasty; TKA

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Currently, over 500 000 total knee arthroplasties (TKAs) are performed in North America annually.[1] Osteoarthritis and destruction of the knee joint remain the primary indications for total joint arthroplasty.[2] Pain is often successfully treated with non-steroidal anti-inflammatory drugs (NSAIDs) which are beneficial early in the disease process; however, once pain becomes severe with significantly compromised physical function and significant radiographic evidence of joint space destruction, patients are offered TKA.[3]

In recent years, gabapentin (a structural analogue of γ-aminobutyric acid), an anticonvulsant that binds to the α2Δ subunit of voltage-dependent calcium channels in activated neurones, has been used widely as an adjunct for the treatment of acute post-surgical pain. Meta-analyses have confirmed the efficacy of gabapentin in reducing postoperative opioid use and pain scores.[4–6] Studies have examined various regimens of co-analgesics after TKA[7 8] but little is known about the use of perioperative gabapentin for TKA on pain and

functional outcomes. A small, open label study found that patients who continued to receive postoperative gabapentin 200 mg three times per day (TID) for 4 days after operation used less morphine and demonstrated improved early functional recovery after TKA.[9] In contrast, the addition of a 600 mg preoperative dose of gabapentin followed by a 2 day regimen of gabapentin 200 mg TID to a robust multimodal regimen did not affect opioid consumption or pain scores after TKA.[10]

As one of the primary goals of TKA is to improve physical function, this surgical model provides an opportunity to study the effects of gabapentin on functional outcomes. Whereas trials have demonstrated a reduction in post-surgical pain with gabapentin,[11–13] it remains to be seen whether this early gain in pain translates into accelerated recovery in-hospital, improved functional status after hospital discharge, or both. Functional measures used herein include both patient-reported outcome measures and performance-based measures of physical function.[14] The *Western Ontario and McMaster Universities Osteoarthritis Index* (*WOMAC LK3.1*)[15 16] is a commonly used patient-reported outcome measure used after TKA. Standardized physical performance measures such as the timed up and go (TUG) test,[17 18] the timed stair test,[19 20] and the six minute walk test (6MWT)[21] have been used to measure function from baseline to 3 months after surgery and all have demonstrated reliability and sensitivity to change within the total joint arthroplasty population.[22]

Neuraxial anaesthetic techniques have become common practice for lower limb arthroplasty.[8] The addition of femoral and sciatic nerve blocks for TKA has demonstrated a reduction in postoperative opioid consumption and pain scores. Previous work showed that a single shot femoral nerve block provided superior analgesia compared with patient-controlled analgesia (PCA) using morphine and pain relief equivalent to that of continuous femoral block and epidural analgesia.[23] The present study evaluated the effect of gabapentin on pain and recovery after TKA, within the context of multimodal analgesia in which all patients received a preoperative spinal anaesthetic (bupivacaine), non-steroidal anti-inflammatory medication (celecoxib), and peripheral femoral and sciatic nerve blocks with ropivacaine.

We do not know the optimal dosing and duration of perioperative gabapentin required to improve functional outcomes, especially in the context of a clinically relevant perioperative analgesic regimen. A meta-analysis suggested that gabapentin may prevent the development of chronic post-surgical pain;[24] however, this hypothesis remains untested. The primary purpose of this randomized, double-blinded, placebo-controlled study was to examine whether in the context of preoperative spinal anaesthesia, femoral and sciatic nerve blocks, and celecoxib co-administration, a 4 day perioperative regimen of gabapentin *vs* placebo improves knee function on performance and self-reported measures of physical function, and movement-evoked pain on postoperative day 4 (POD4) and at 6 weeks and 3 months after surgery. Secondary endpoints examined whether this regimen improves in-hospital knee range of motion (POD1–4) pain scores at rest and opioid consumption.

## Methods

### Patient sample and recruitment procedures

The study was approved by the Sunnybrook Health Science Centre Research Ethics Board and all patients gave informed written consent to participate. Patients between the ages of 18 and 75 years with an ASA physical status score of I, II, or III undergoing TKA were eligible to participate. Patients were not eligible if they had a known allergy to any of the medications being used, a history of drug or alcohol abuse, a history of being on chronic pain medications (e.g. slow-release preparations of opioids), rheumatoid arthritis, a psychiatric disorder, a history of diabetes with impaired renal function (creatinine $>106$), a BMI of $>40$, or were unable or unwilling to use PCA.

All subjects were screened in order to ensure eligibility and patients were recruited at the preoperative assessment $\sim$1–2 weeks before surgery. At that time, the study protocol, use of the PCA pump, and the visual analogue scale (VAS), a 0–10 cm scale (with endpoints labelled 'no pain' and 'worst pain possible pain'), were explained. Baseline physical function measures and psychosocial questionnaires were completed at the preoperative assessment or on the morning of surgery before the procedure.

### Drug preparation, dispensing, and randomization

Gabapentin and placebo medications were encapsulated in identically coloured gelatin capsules and packaged in identical individual blister packs by the Sunnybrook Health Sciences Centre Investigational Pharmacy in order to maintain double-blinded conditions. The placebo capsules contained a mixture of 50% cellulose and 50% lactose monohydrate. A computer-generated randomization schedule was used to assign patients at random, in blocks of six, to one of the two treatment groups. The schedule was created by the hospital investigational pharmacy using randomization.com (http://www.jerrydallal.com/random/randomize.htm). The investigational pharmacy was otherwise not involved in the clinical care of the patients or in the conduct of the trial. The randomization schedule was kept in the pharmacy and none of the investigators had access to it. The pharmacy dispensed the capsules according to the randomization schedule when the investigators informed them that a patient had been recruited into the trial. Researchers were also blind to drug assignment during data analysis.

### Pre- and intra-operative anaesthesia care

Standard practice at the Sunnybrook Holland Orthopaedic and Arthritic Centre is for patients to continue taking celecoxib until surgery. On the day of surgery, all patients received celecoxib 400 mg p.o., 2 h before operation. Patients were randomly assigned to receive either gabapentin 600 mg p.o. or placebo p.o. at the same time they received the celecoxib. Two hours after study medication ingestion, patients were transferred to the regional anaesthesia block area where an i.v. cannula was inserted and an infusion of i.v. lactated Ringer's solution