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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

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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 was started at a rate of 100 ml h^{-1}. Blood pressure, ECG, and oximetry were monitored. Midazolam 1–3 mg i.v. was administered. Femoral and sciatic nerve blocks were performed using a nerve stimulator/ultrasound technique. A motor-evoked response at a current of $<$0.5 mA was accepted as an endpoint of stimulation. Ropivacaine 0.5%, 20 ml was deposited adjacent to each nerve. Spinal anaesthesia was performed in the lateral decubitus or sitting position using 25 g Whitacre needle. Ten milligrams of 0.5% hypobaric bupivacaine with 10 μg of fentanyl was injected. In the operating theatre, sedation was provided with i.v. propofol infusion (25–100 μg kg min^{-1}) until the end of surgery. Surgical techniques were standardized at the Holland Orthopaedic and Arthritic Centre. The attending anaesthesiologist was not involved in the patients' evaluation after operation.

Postoperative anaesthesia care

Patients were asked to record their rest and movement-evoked pain intensity using a 10 cm VAS commencing in the postanaesthetic care unit (PACU) after surgery upon being given the i.v. PCA morphine device, and continuing every 6 h for the next 24 h. The PCA pump was set to deliver morphine 1 mg per demand with a 5 min lockout interval and no background infusion. All patients were instructed to maintain their pain intensity at $<$4/10 on the VAS. If the VAS pain score at rest was rated 5 cm or greater on two consecutive 4 h assessments, the dose of i.v. PCA morphine was increased to 1.5 mg per demand. At each time point when pain was measured, patients were also assessed for the presence of nausea, vomiting, and pruritus and the severity of sedation [0=alert, 1=mild (occasionally drowsy, easy to arouse), 2=moderate (frequently drowsy, easy to arouse), 3=severe (somnolent, difficult to arouse), S=normal sleep, easy to arouse].

Upon discharge from the PACU, all patients received a standard postoperative regimen of celecoxib 200 mg q12h and a morphine i.v. PCA device for 24 h. Patients received either gabapentin 200 mg TID or placebo TID as per the preoperative randomization allocation starting 8 h after the preoperative dose and continuing for 4 days. Oxycontin 5 mg q8h was started at 08:00 on the morning after surgery to facilitate the termination of PCA morphine at 24 h. After operation, all patients were managed using a standardized knee care pathway that included daily physiotherapy treatment. Patients were permitted to be full weight-bearing and participated in a progressive programme of range of motion, strengthening exercises, and functional training.

The Departments of Anaesthesiology, Orthopaedic Surgery, Rehabilitation Science and Psychology collaborated on the current project, and each unit was instrumental in selecting the various outcome measures and in ensuring appropriately qualified people collected the data. Fully qualified and trained physiotherapists at the Holland Orthopaedic and Arthritic Centre collected the physiotherapy data and our study coordinators (certified RNs and research coordinators) were responsible for the collection of Pain data and follow-up questionnaire data. Blinding was maintained throughout the study until the code was broken upon the completion of our statistical analysis.

Questionnaires

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK3.1)

The WOMAC is a 24-item Likert scale that assesses the extent to which patients with knee, hip, or both osteoarthritis experience pain, stiffness, and physical functional impairment.[15 16] The WOMAC comprises three subscales, namely pain (5 items), stiffness (2 items), and physical function (17 items). For each item, patients are asked to rate the extent to which they experience pain/stiffness/physical limitations on a scale ranging from 0 (none) to 4 (extreme). Total scores range from 0 to 20 for the pain subscale, 0 to 8 for the stiffness subscale, and 0 to 68 for the physical function subscale with higher scores indicating worse pain/stiffness/physical limitations. The WOMAC subscales have very good internal consistency (α=0.86–0.95),[25] adequate test–retest reliability (intraclass correlation coefficient=0.74–0.95),[26 27] good sensitivity and responsiveness to change over time,[28–30] and also adequate face,[15] construct[30–32], and criterion[32–34] validity. Important within-patient change scores have been estimated to be 4.5 for pain and 9 for physical function.[35 36]

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item Likert scale that assesses symptoms of depression (7-item subscale) and anxiety (7-item subscale).[37] The HADS is the preferred measure of anxiety and depressive symptoms for non-psychiatric hospital patients. For each item, patients are asked to check the answer that most closely describes how they have been feeling in the past week on a scale from 0 to 3. Total scores for each subscale range from 0 to 21, with higher scores indicating higher levels of anxiety or depression. The internal consistency of the depression (α=0.67–0.90) and anxiety (α=0.68–0.93) subscales of the HADS is adequate.[38] The HADS also has good discriminant and convergent validity and also specificity and sensitivity in detecting clinical significant levels of depression and anxiety.[38] When administered on POD4, patients were asked to report how they have been feeling while in-hospital.

Functional outcomes

Knee range of motion, the timed get up and go test, the stair test, and the 6MWT were used to evaluate functional performance.

Knee range of motion

Active assisted knee flexion and active knee extension were recorded. Immediately after the measurement of knee flexion, patients were asked to rate the intensity of their pain. Knee range motion has been shown to have good reliability

among patients with knee osteoarthritis.[22] Range of motion was measured pre-surgery and daily on PODs 1, 2, 3, and 4.

Timed get up and go test

Patients were asked to rise from a standard arm chair, walk at a safe and comfortable pace for 3 m, and then return to a sitting position in the chair.[17 18] Time to complete the test in seconds, use of an armrest to get up and sit down, and pain intensity at the site of surgery immediately after the test were recorded. This test was administered pre-surgery, on POD4 (for those who were able to perform it), and 6 weeks and 3 months post-surgery. An important within-patient change has been estimated to be ~2.5 s.[22 39]

Stair test

Patients were asked to ascend and descend one flight of nine stairs in their usual manner, at a safe and comfortable pace.[19 40] Test completion, length of time to complete the test, aids used (crutches, cane, railing), ascending and descending pattern, and also pain intensity at the site of surgery were recorded. This test was administered pre-surgery, on POD4 (for those who were able to perform it), and 6 weeks and 3 months post-surgery. An important within-patient change has been estimated to be ~5.5 s.[22 39]

Six minute walk test

Patients were asked to walk as far as possible during 6 min, with the option to stop and rest as needed during the test.[41–43] Standardized encouragement was offered to all patients every 60 s as research has shown that encouragement improves performance.[44] Total distance walked, test completion, and pain intensity at the site of surgery were recorded. This test was administered pre-surgery and at 6 weeks and 3 months post-surgery. An important within-patient change has been estimated to be ~62 m.[22 39]

Sample size estimate

There is a paucity of information available concerning the magnitude of a clinically important between-group difference for performance measures. For this reason, our sample size estimate was based on the WOMAC physical function scores. Goldsmith and colleagues have suggested that for self-report measures an important between-group difference is less than an important within-patient change.[45] Applying this principle to the WOMAC physical function scale, we specified an important between-group difference to be ~5-points at 4 days and 6 weeks and 4-points at 3 months post-arthroplasty. The power was set at 0.80 and the overall Type I error probability at 0.05 corrected to 0.0167 owing to comparisons at three time points (POD4, 6 weeks, and 3 months). Applying these assumptions yielded an approximate sample size of 72 subjects per group. Allowing for an incomplete data percentage of 20%, 92 subjects per group or 184 subjects in total were required.

Statistical analysis

Given a repeated measures study design, the likelihood of missing data, correlated errors within individuals, and heterogeneity among occasion variances (i.e. over time), we applied Generalized Estimating Equations to test for differences in the TUG test, the stair test, and the 6MWT between the Groups G and P. Dependent variables were the outcome measures assessed at multiple time points (i.e. TUG test, stair test, and 6MWT). The independent variable was treatment group (gabapentin or placebo) and the covariates were gender, age, and the pre-surgery values for the dependent variable of interest. We applied an autoregressive correlation structure for cumulative morphine consumption and an unstructured correlation structure for all other dependent variables. An effect was considered statistically significant at $P \leq 0.05$ and we performed intention-to-treat analyses. We did not impute values when data were missing. All analyses were conducted using STATA version 13.0 (STATA Corp., College Station, TX, USA).

Results

Recruitment and retention of patients

Patients were recruited between November 2007 and March 2011. The CONSORT[46] flow chart outlining the recruitment and retention of study patients is shown in Fig. 1. Overall, 650 patients were approached for participation, 438 patients declined participation and 212 patients consented to participate in the study, 33 of whom were excluded or withdrew before randomization. Of the 179 patients randomly assigned to receive gabapentin (Group G) or placebo (Group P), 165 patients remained in the study 24 h after operation, 77 of 84 patients (92%) in Group P, and 88 of 95 (93%) patients remained in Group G. The reasons for withdrawal/dropout in Group P at 24 h were as follows: three patients had their surgery cancelled after the study medications were given, two patients were removed by attending physicians after being given general anaesthesia, and two patients asked to be removed on POD 1 because they were unhappy with their pain control. The reasons for withdrawal/dropout in Group G at 24 h were as follows: four patients had their surgery cancelled after the study medications were given and three patients asked to be removed early on POD1 because they were unhappy with their pain control. On POD4, 150 patients were eligible to complete the physiotherapy measures. Six weeks after surgery data were collected from 76 patients in the placebo group (one patient was lost to follow-up) and 81 patients in the gabapentin group (seven patients were lost to follow-up). At 3 months after surgery, data were collected from 76 patients in the placebo group and 79 patients in the gabapentin group (two patients were lost to follow-up).

Baseline characteristics and clinical variables

The two groups were comparable with respect to age, sex, BMI, ASA status, duration of surgery, and all self-report scales and physical functional assessment measures (Table 1).

Performance and patient-report measures/primary outcomes

Performance outcomes on the TUG test, the stair test, the 6MWT, and WOMAC function scores are presented in Table 2 for the POD4, 6 week, and 3 month assessments. Significant

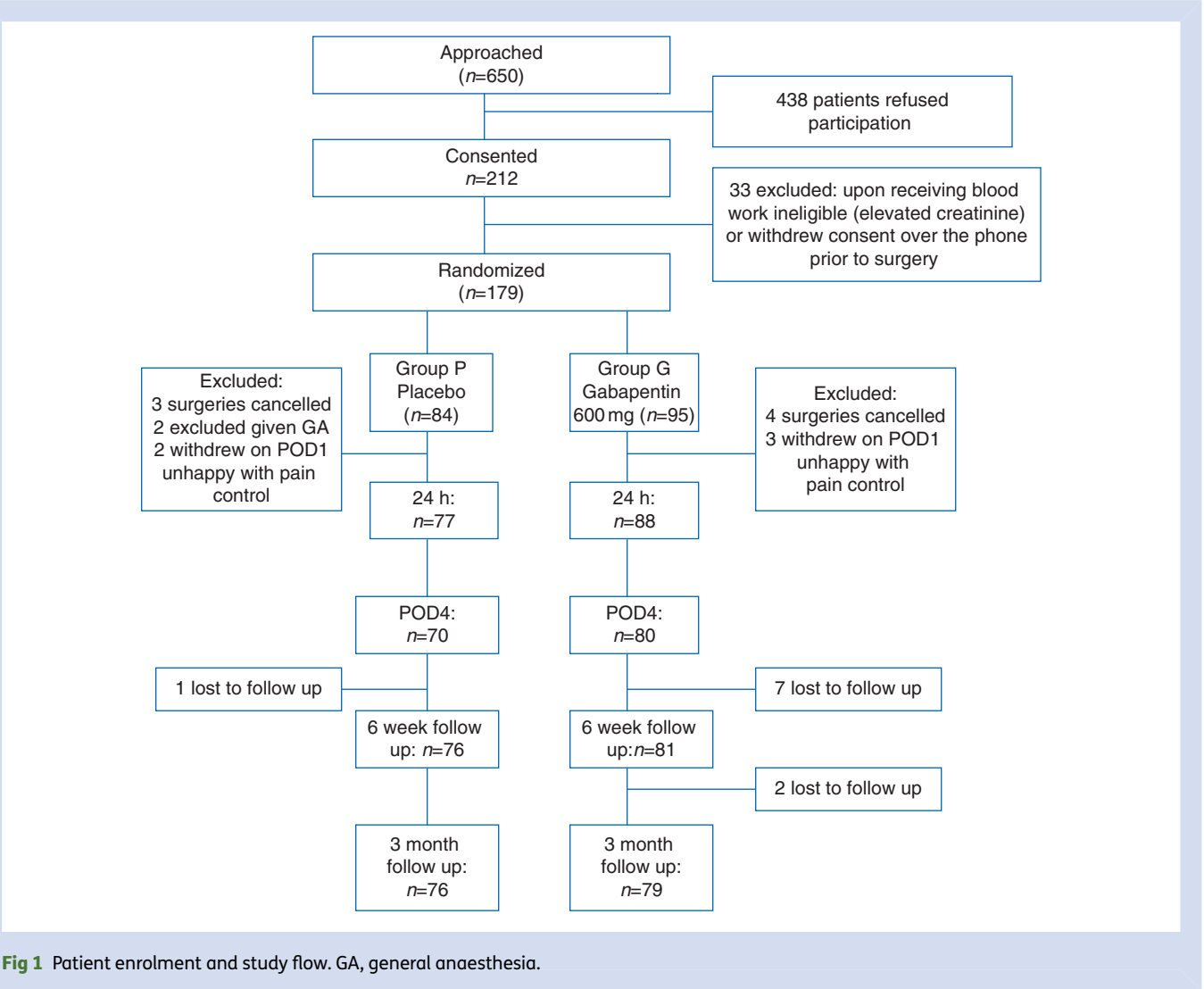

Fig 1 Patient enrolment and study flow. GA, general anaesthesia.

differences were not found on any performance-based measure at these time points nor was there a difference in patient-reported function across the time points. Moreover, the confidence intervals (CIs) on the WOMAC physical function between-group difference at 6 weeks and 3 months did not include our declared clinically important difference value of 5 points.

Table 3 presents the pain scores associated with each functional measure and also the WOMAC pain scores for the POD4, 6 week, and 3 month assessments. Significant differences were not found on any pain measure associated with the three performance-based measures at any point in the study.

Secondary outcomes

Opioid consumption

Cumulative morphine consumption was significantly lower in the gabapentin group compared with the placebo group at 18 and at 24 h after TKA ($P<0.0125$) (Fig. 2). Pain scores did not differ significantly at rest or with movement between the two groups over the first 24 h.

In-hospital knee range of motion

Table 4 shows the knee flexion (range of motion) and associated pain scores, occasion-specific sample sizes, unadjusted group means and standard errors, and adjusted between-group differences with accompanying 95% CI and *P*-values. The gabapentin group had significantly better active assisted knee range of motion during the first 3 days of hospital rehabilitation compared with controls; however, this difference was not maintained at subsequent assessments. Pain scores were not different between the two groups during the physiotherapy sessions.

Adverse effects

On POD1, the placebo group had a higher incidence of nausea (Group P 34% *vs* Group 30% G) ($P=0.013$) and pruritus (Group P 31% *vs* Group G 4%) ($P=0.007$). On POD3, the placebo group also reported more dizziness (Group P 15% *vs* Group G 2%) ($P=0.025$) compared with the gabapentin group. Significant differences were not found at any point

during the hospital stay with respect to sedation severity or the incidence of vomiting. No other adverse events were documented.

Table 1 Patient, baseline characteristics and duration of surgery

Variable	Group		*P*-value
	Placebo (*n*=84)	Gabapentin (*n*=95)	
Age (yr)	62.8 (7.4)	62.9 (6.3)	0.92
Sex (male/female)	47/37	42/53	0.11
Body mass index (kg m^{-2})	31.1 (5.6)	32.3 (5.1)	0.13
Duration of surgery (min)	71.3 (22.0)	71.8 (19.7)	0.87
ASA class			n.s.
I	8	8	
II	59	68	
III	17	19	
Knee flexion range (°)	113.6 (14.1)	112.3 (17.1)	0.58
Stair test (s)	20.8 (9.5)	22.4 (11.3)	0.31
Stair pain (0–10)	4.4 (2.3)	4.6 (2.5)	0.58
TUG (s)	12.5 (4.5)	12.2 (4.7)	0.66
TUG pain (0–10)	3.4 (2.3)	3.2 (2.3)	0.56
6MWT (m)	356 (131)	358 (136)	0.92
6MWT pain (0–10)	5.5 (2.3)	5.0 (2.3)	0.14
WOMAC pain (0–20)	9.8 (2.9)	9.8 (3.3)	>0.99
WOMAC stiffness (0–8)	4.3 (1.6)	4.7 (1.6)	0.10
WOMAC physical function (0–68)	32.6 (9.2)	34.4 (12.3)	0.27
HADS—Anxiety (0–21)	6.0 (3.8)	6.0 (3.1)	>0.99
HADS—Depression (0–21)	4.5 (2.5)	4.2 (2.6)	0.43

Hospital Anxiety and Depression Scores on POD4, 6 weeks, and 3 months

HADS anxiety scores did not differ between groups on POD4 [G: 5.9 (2.9), P: 5.2 (3.3)] and 6 weeks [G: 5.2 (3.5), P: 4.3 (3.5)] or 3 months [G: 3.9 (3.2), P: 3.5 (2.8)] after TKA. Similarly, HADS depression scores did not differ between groups on POD4 [G: 4.6 (3.0), P: 4.8 (3.1)] and 6 weeks [G: 4.2 (2.9), P: 3.8 (3.0)] and 3 months [G: 5.2 (2.2), P: 5.6 (2.4)] after surgery ($P>0.05$).

Discussion

The pain-relieving and opioid-sparing effects of gabapentin have been studied more frequently among patients receiving only general anaesthesia than in those receiving regional anaesthesia. The present study was designed with the primary aim of examining whether a 4 day perioperative regimen of gabapentin within the context of spinal anaesthesia, peripheral nerve blocks (femoral and sciatic), perioperative administration of NSAIDs (celecoxib), and i.v. PCA morphine for 24 h would improve knee function and functional recovery post-discharge. The 600 mg preoperative dose of gabapentin was chosen, given a study that followed patients undergoing lumbar discectomy suggested that the optimal preoperative dose of gabapentin for optimal acute postoperative pain relief was 600 mg; at higher doses (900 and 1200 mg), an analgesic ceiling effect was observed, in which patients exhibited more side-effects without an additional reduction in acute pain.[47] At the time of commencement of this trial, no study had been published using gabapentin in an awake population with a robust multimodal regimen which included preoperative spinal anaesthesia, NSAIDs (celecoxib), and peripheral femoral

Table 2 Performance and patient-reported physical function measures. *Negative difference favours gabapentin group; †positive difference favours gabapentin group. WOMAC scores: Physical Function Subscale. *P*-value reflects ANCOVA

	Group				Adjusted difference	
	Placebo		Gabapentin		(95% CI)	*P*-value
	Unadjusted		Unadjusted			
	n	Mean (SE)	*n*	Mean (SE)		
TUG* (s)						
POD4	66	42.6 (3.6)	71	40.1 (3.4)	−3.0 (−8.4, 2.5)	0.286
6 weeks	77	13.5 (0.9)	81	13.8 (0.7)	−0.1 (−5.2, 4.9)	0.956
3 months	71	10.6 (0.7)	79	10.4 (0.5)	−0.5 (−5.7, 4.9)	0.850
Stair test* (s)						
POD4	57	56.9 (4.4)	62	57.5 (3.3)	−2.3 (−8.4, 3.7)	0.451
6 weeks	72	22.7 (1.5)	79	24.2 (1.5)	0.6 (−4.8, 6.0)	0.829
3 months	69	15.8 (1.5)	77	18.4 (1.5)	0.2 (−5.2, 5.7)	0.941
Six minute walk† (m)						
6 weeks	75	333 (16)	76	363 (15)	27.5 (−5.9, 60.9)	0.107
3 months	69	436 (15)	78	444(12)	9.4 (−24.6, 43.4)	0.588
WOMAC function* (0–68)						
POD4	44	35.3 (1.4)	51	33.8 (1.3)	−2.2 (−6.3, 2.0)	0.302
6 weeks	72	19.9 (1.3)	81	23.8 (1.4)	3.1 (−0.2, 6.5)	0.065
3 months	76	13.6 (1.2)	79	15.2 (1.3)	1.0 (−2.2, 4.3)	0.540

Table 3 Performance-related numeric pain rating scale (0–10) scores. *Negative difference favours gabapentin group; † positive difference favours gabapentin group. *P*-value reflects ANCOVA

	Group				Adjusted difference	
	Placebo		Gabapentin		(95% CI)	*P*-value
	Unadjusted		Unadjusted			
	n	Mean (SE)	*n*	Mean (SE)		
TUG—pain*						
POD4	65	4.2 (0.3)	72	4.3 (0.3)	0.1 (−0.5, 0.7)	0.836
6 weeks	74	1.7 (0.2)	81	2.0 (0.2)	0.2 (−0.3, 0.8)	0.436
3 months	72	0.7 (0.2)	78	0.8 (0.2)	0.1 (−0.5, 0.7)	0.690
Stair test—pain*						
POD4	61	4.0 (0.3)	63	4.3 (0.3)	0.2 (−0.4, 0.9)	0.488
6 weeks	74	2.2 (0.2)	77	2.8 (0.2)	0.4 (−0.2, 1.0)	0.154
3 months	69	1.2 (0.2)	76	1.6 (0.2)	0.3 (−0.3, 0.9)	0.299
Six minute walk—pain†						
6 weeks	72	2.9 (0.2)	73	2.9 (0.2)	0.2 (−0.4, 0.8)	0.475
3 months	76	1.2 (0.2)	75	1.4 (0.2)	0.2 (−0.4, 0.9)	0.435
WOMAC—pain* (0–20)						
POD4	69	8.5 (0.4)	80	8.3 (0.3)	−0.5 (−1.4, 0.5)	0.342
6 weeks	76	6.2 (0.3)	81	7.3 (0.4)	1.0 (0.1, 1.9)	0.039
3 months	76	3.5 (0.5)	79	4.2 (0.4)	0.7 (−0.2, 1.7)	0.133

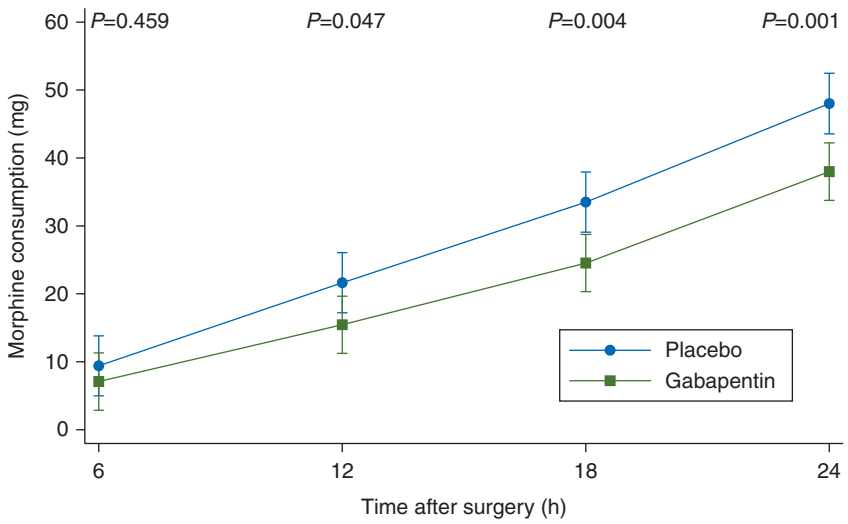

Fig 2 Twenty-four-hour cumulative morphine consumption [mean (95% CI)].

and sciatic nerve blocks and data were available which demonstrated the effectiveness of this regimen for the reduction of opioid consumption and improvement in early knee function after TKA.[9] The present study did not find significant differences between gabapentin and placebo groups in the primary measures of function (both physical and patient reported) on POD4 and 6 weeks or 3 months after TKA (Tables 2 and 3). Furthermore, pain scores at 6 weeks and 3 months did not differ between groups with respect to each performance-based measure. Consistent with previous literature,[9 12] this study demonstrated a 24 h reduction in opioid consumption and an overall improvement in active assisted knee flexion to 4 days after operation while patients were receiving gabapentin (Fig. 2 and Table 4).

The possibility that gabapentin may have preventive perioperative analgesic effects (as defined by demonstrating pain reduction, improved function, or both when compared with controls >5.5 biological half-life after the medication)[48] has been reported in previous studies.[49 50] A published meta-analysis found that 50% of the published trials to date

Table 4 Knee flexion range of motion and pain scores. *Negative difference favours gabapentin group; †positive difference favours gabapentin group. *P*-value reflects ANCOVA

	Group				Adjusted difference	
	Placebo		Gabapentin		(95% CI)	*P*-value
	Unadjusted		Unadjusted			
	n	Mean (SE)	*n*	Mean (SE)		
Knee flexion range† (°)						
POD1	76	55.1 (2.2)	83	60.8 (1.8)	5.9 (0.9, 11.0)	0.020
POD2	74	62.8 (1.9)	85	69.1 (1.4)	7.9 (2.9, 13.0)	0.002
POD3	77	75.0 (1.6)	84	79.5 (1.5)	5.9 (0.9, 10.9)	0.021
POD4	70	80.9 (1.3)	80	83.8 (1.3)	4.1 (−1.1, 9.3)	0.123
6 weeks	74	102.5 (2.1)	81	105.1 (1.4)	0.9 (−4.2, 6.0)	0.724
3 months	74	115.2 (1.6)	79	116.2 (1.3)	0 (−5.1, 5.1)	0.997
Knee flexion pain* (0–10)						
POD1	76	6.4 (0.2)	83	5.8 (0.3)	−0.4 (−1.2, 0.4)	0.336
POD2	74	5.6 (0.3)	85	6.0 (0.2)	0.8 (0, 1.6)	0.050
POD3	77	5.7 (0.3)	84	5.5 (0.3)	0.2 (−0.6, 1.0)	0.665
POD4	70	5.5 (0.3)	80	5.6 (0.3)	0.5 (−0.3, 1.3)	0.255
6 weeks	70	2.3 (0.2)	75	2.6 (0.2)	0.3 (−0.6, 1.2)	0.493
3 months	70	1.0 (0.2)	74	1.3 (0.2)	0.6 (−0.2, 1.5)	0.139

which examined the use of gabapentin for the reduction of chronic post-surgical pain were positive, but clearly more evidence is needed to determine whether this class of medications has such reported preventive effects.[24] Furthermore, others have suggested that early reductions in acute post-surgical pain could lead to improvements in early mobilization and this 'head start' in activity might improve the long-term trajectory of treated patients.[51 52] We designed this trial to determine whether gabapentin would demonstrate preventive analgesic effects and included time points well beyond the physiologically active duration of the medication (i.e. 6 weeks and 3 months after surgery). The present results do not support the hypothesis of superior functional performance long-term in the gabapentin *vs* the placebo group.

The results of the present study confirm open label evidence[9] that perioperative gabapentin when added to celecoxib for 4 days after operation reduces opioid consumption and leads to an improvement in active assisted knee flexion while patients are in-hospital. Consistent with previous results,[9] there was no difference in opioid consumption between the two groups in the first 12 h after surgery, which demonstrates the effectiveness of the femoral and sciatic nerve blocks in the first 8–12 h after total knee replacement. Active assisted knee flexion in the gabapentin group was ~6.1° greater than the placebo group during the first 4 days after surgery. The significantly greater incidence of pruritus and nausea found on POD1 in the placebo group is associated with increased morphine use by this group and is consistent with previous studies.[53]

Patients self-report measures of anxiety and depressive symptoms throughout the trial were unaffected by gabapentin administration. Studies have shown that a high level of preoperative anxiety is a risk factor for acute post-surgical pain[54] and is associated with the development of chronic post-surgical pain.[55] In a select population of highly anxious females (i.e. baseline anxiety >5/10) undergoing major surgery, 1200 mg of gabapentin significantly reduced preoperative anxiety and pain catastrophizing before major surgery.[56] The dosing regimen of the present study (i.e. 600 mg) and the low baseline levels of anxiety symptoms may explain the absence of an anxiolytic effect of gabapentin.

This is the first adequately powered study to compare the efficacy of gabapentin *vs* placebo for recovery of physical function over three periods (POD4, 6 weeks, and 3 months) after TKA. Although negative for such outcomes, a reduction in cumulative opioid consumption and superior in-hospital range of motion recovery were evident. These latter findings are consistent with the bulk of the published literature in patients undergoing surgeries associated with moderate/severe post-surgical pain. Other populations and regimens examining the use of perioperative gabapentin are needed. The present results are specific to our multimodal analgesic regimen and cannot be generalized to the same surgery with alternative perioperative pain regimens or other surgeries performed under general anaesthesia. Furthermore, given the low rate of consent (32%) of patients that were approached and the 14% of patients that were lost to follow-up, the generalizability of this study may be limited.

In conclusion, a single preoperative dose of gabapentin 600 mg, co-administered with celecoxib, and followed by 4 days of gabapentin 200 mg TID, decreased immediate postoperative analgesic requirements and resulted in improved range of motion while patients were taking active medication and undergoing in-hospital rehabilitation. Gabapentin provided

no improvement in pain or physical function on POD4, 6 weeks, or 3 months after surgery. The effects on functional outcomes based on the continued use of gabapentin into the post-discharge period need to be assessed in future work. Furthermore, future studies should continue to explore potential patient populations (i.e. patients with obstructive sleep apnoea, chronic pain patients, opioid dependent, etc.) that may benefit from the early opioid-sparing benefits and the early improvement of physical function associated with the administration of perioperative gabapentin.

Authors' contributions

H.C. is the primary author of this manuscript and responsible for designing the study and reviewing the analysis of the data, and has approved the final manuscript. J.K. is a co-author of the manuscript responsible for helping to design the study, writing some of the manuscript, and approving the final manuscript. C.McC. is a co-author of the manuscript responsible for overseeing the study at the Holland Centre, writing some of the manuscript, and approving the final manuscript. P.S. is the biostatistician responsible for the analysis of the data and has approved the final manuscript. D.K. contributed to the writing of the manuscript, helped to develop the initial protocol, and has approved the final manuscript. G.P. contributed to the manuscript, helped with data analyses, and approved the final manuscript. I.T.A. is a co-author of the manuscript, responsible for overseeing the study at the Holland Centre, writing some of the manuscript, and approving the final manuscript. J.G. is an orthopaedic surgeon, contributed to the initial design of the study, and contributed to and approved the final manuscript. J.K. is the senior author and was involved in the design of the study, analysis of the results, and writing of the manuscript. He has approved the final manuscript.

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Declaration of interest

None declared.

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