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Pregabalin reduces postoperative opioid consumption and pain for 1 week after hospital discharge, but does not affect function at 6 weeks or 3 months after total hip arthroplasty

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Abstract

Background: This study examined whether a perioperative regimen of pregabalin added to celecoxib improved pain scores and functional outcomes postdischarge up to 3 months after total hip arthroplasty (primary outcome) and acute postoperative pain and adverse effects (secondary outcomes).

Methods: One hundred and eighty-four patients were enrolled in a randomized, double-blind, placebo-controlled study. Two hours before receiving a spinal anaesthetic and undergoing surgery, patients received celecoxib 400 mg p.o. and were randomly assigned to receive either pregabalin 150 mg p.o. or placebo p.o. After surgery, patients received pregabalin 75 mg or placebo twice daily in hospital and for 7 days after discharge. Patients also received celecoxib 200 mg every 12 h for 72 h and morphine i.v. patient-controlled analgesia for 24 h. Pain and function were assessed at baseline, 6 weeks, and 3 months after surgery.

Results: There was no difference between groups in physical function or incidence and intensity of chronic pain 3 months after total hip arthroplasty. The pregabalin group used less morphine [mean (SD): 39.85 (28.1) mg] than the placebo group [54.01 (31.2) mg] in the first 24 h after surgery ($P<0.01$). Pain scores were significantly lower in the pregabalin group *vs* the placebo group on days 1–7 after hospital discharge, and the pregabalin group required less adjunctive opioid medication (Percocet) 1 week after hospital discharge ($P<0.05$).

Conclusions: Perioperative administration of pregabalin did not improve pain or physical function at 6 weeks or 3 months after total hip arthroplasty. Perioperative administration of pregabalin decreased opioid consumption in hospital and reduced daily pain scores and adjunct opioid consumption for 1 week after discharge.

Key words: multimodal analgesia; pain; postdischarge pain; pregabalin; total hip arthroplasty

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Editor's key points

- Maximizing functional recovery after hip arthoplasty, with minimal pain, is an important aim. Pregablin has been used in the perioperative period, with some evidence of acute analgesic benefit.
- Pregabalin reduced pain and analgesia for 1 week after surgery but not longer.
- Further studies are needed of pregabalin in acute, subacute, and chronic pain after surgery.

Total hip arthroplasty (THA) is a surgical procedure indicated in the management of severe, degenerative osteoarthritis and proximal femoral fractures. More than 300 000 THAs are performed each year in the USA,[1] with this number expected to double by 2025 and quadruple by 2040.[2] Although intended to reduce pain, improve function, and benefit quality of life, THAs are associated with moderate-to-severe postoperative pain, which can persist and evolve into chronic pain.[3]

The management of acute pain after THA has been well studied and involves multimodal analgesia, including opioids and other adjuncts. This serves well in hospital; however, postoperative pain in surgical patients after hospital discharge remains a significant challenge. A recent national study in the USA revealed that 80% of patients experience acute pain after surgery and that this pain was more common after discharge than before.[4] Additional evidence reveals that postoperative pain for surgical patients can persist for 2–6 weeks after discharge from hospital and can limit participation in daily activities.[5–7] Furthermore, it has been shown that poorly controlled postoperative pain can lead to the development of chronic pain.[8]

Pregabalin is a structural analogue of γ-aminobutyric acid (GABA) that acts on the $\alpha_2\delta$ subunit of voltage-dependent calcium channels. It was initially introduced in 2004 as an anticonvulsant.[9] Compared with its predecessor, gabapentin, pregabalin possesses superior oral absorption and bioavailability.[10] More recently, like gabapentin, pregabalin has attracted much interest as an adjunct in the management of neuropathic and postoperative pain. This has been reflected in several meta-analyses suggesting that pregabalin reduces postoperative opioid consumption and postoperative nausea and vomiting.[11 12] There is also the suggestion that perioperative pregabalin may prevent the development of chronic postsurgical pain.[13] The literature regarding this, however, is equivocal, as pregabalin has been shown to reduce acute postoperative pain and opioid consumption in spine,[14 15] breast,[16 17] and gynaecological procedures,[18 19] but not in laparoscopic cholecystectomies,[20] ankle surgery,[21] or cosmetic surgery.[22] Furthermore, perioperative pregabalin has also been shown to reduce chronic pain and improve functioning in total knee arthroplasty[23] and lumbar discectomy patients.[24] Others have pointed to a publication bias highlighting unpublished data that failed to show a difference between pregabalin and placebo for the prevention of chronic postsurgical pain.[25]

The literature on the effects of pregabalin for THA is sparse. A prospective, double-blind, randomized, placebo-controlled study involving 120 patients demonstrated that a preoperative dose of 300 mg of pregabalin reduced postoperative morphine requirements compared with placebo.[26] In addition, compared with patient-controlled analgesia using morphine alone, a multimodal analgesic regimen that included pregabalin 75 mg before surgery and pregabalin 75 mg twice daily (BID) for 48 h produced equal levels of satisfactory pain control and fewer adverse effects.[27] However, there is a lack of consensus regarding the appropriate dose or timing of pregabalin administration required to improve acute and postdischarge postoperative pain and physical functioning after surgery.

We conducted this randomized, double-blind, placebo-controlled study to examine whether the addition of pregabalin to our perioperative THA analgesic regimen in the perioperative period and for 7 days after discharge improves pain and functional outcomes up to 3 months after surgery.

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. Patient's between the ages of 18 and 80 yr with an ASA physical status score of I, II, or III undergoing primary total hip arthroplasty 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), short-acting opioids at a dose greater than 30 mg day^{-1} of oral morphine equivalents, anticonvulsant medications, rheumatoid arthritis, a psychiatric disorder, a history of diabetes with impaired renal function (creatinine >104 μmol/L), a BMI of >40 kg m^{-2}, or were unable or unwilling to use patient-controlled analgesia (PCA).

All subjects were screened in order to ensure eligibility, and patients were recruited at the preoperative assessment approximately 1–2 weeks before surgery. At that time, the study protocol, use of the PCA pump, and an 11-point numerical rating scale (NRS) for pain (0='no pain' and 10='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

Pregabalin capsules were provided by Pfizer Canada Inc., 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-blind 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, which 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 intraoperative anaesthesia care

Standard practice at the Sunnybrook Holland Orthopedic 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 surgery. Patients were randomly assigned to receive either pregabalin 150 mg p.o. or placebo p.o. at the same time they

received the celecoxib. Two hours after ingestion of the study medication, patients were transferred to the regional anaesthesia block area, where an i.v. cannula was inserted and an i.v. infusion of 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. Spinal anaesthesia was performed in the lateral decubitus or sitting position using a 25 gauge Whitacre needle. Hypobaric bupivacaine 0.5% (10 ml) with fentanyl 10 μg was injected. In the operating room, sedation was provided with propofol infusion (25–100 μg kg^{-1} min^{-1} i.v.) until the end of surgery. Surgical techniques were standardized at the Holland Orthopaedic and Arthritic Centre. The attending anaesthetist was not involved in the patients' postoperative evaluation.

Postoperative anaesthesia care

Patients were asked to record their resting and movement-evoked pain intensity using a 10 cm NRS, commencing in the postanaesthetic care unit 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 on demand with a 5 min lockout interval and no background infusion. All patients were instructed to maintain their pain intensity at less than 4/10 on the NRS. If the NRS pain score at rest was rated 5 cm or greater on two consecutive 4 hourly assessments, the dose of i.v. PCA morphine was increased to 1.5 mg per demand. Once the patients' pain was reported as ≤4/10, the i.v. PCA pump setting returned to 1.0 mg per demand. At each time point when pain was measured, patients were also assessed for the presence of nausea, vomiting, pruritus, and the severity of sedation [0=alert, 1=mildly sedated (occasionally drowsy, easy to arouse), 2=moderately sedated (frequently drowsy, easy to arouse), 3=severely sedated (somnolent, difficult to arouse), S=normal sleep, easy to arouse].

Upon discharge from the postanaesthesia care unit, all patients received a standard postoperative regimen of celecoxib 200 mg every 12 h and a morphine i.v. PCA device for 24 h. Patients received either pregabalin 75 mg BID or placebo BID according to the preoperative randomization allocation, starting 8 h after the preoperative dose and continuing throughout their hospital stay and for 7 days after discharge. Oxycontin 5 mg every 8 h was started at 08.00 h on the morning after surgery to facilitate the termination of PCA morphine at 24 h. After surgery, all patients were managed using a standardized hip arthroplasty care pathway that included daily physiotherapy treatment. Patients were permitted to be fully 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 present project; each unit was instrumental in selecting the various outcome measures and in ensuring that appropriately qualified people collected the data. Fully qualified and trained physiotherapists at the Holland Orthopedic 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.

Follow-up data collection at 7 days, 6 weeks, and 3 months after discharge

Patients were discharged home with a diary to make note of adverse reactions that might be a result of the study medication. Every day for up to 7 days after the patient was discharged from hospital, the research coordinator followed up with the patient via a telephone call to inquire about pain intensity, physical function, and adverse reactions. Patients were expected to return to the Holland Arthritic and Orthopedic Centre at 6 weeks and 3 months, at which time the battery of physical function tests and psychological questionnaires were re-administered.

Questionnaires

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK3.1)[28 29] is a 24-item Likert scale that assesses the extent to which patients with knee or hip osteoarthritis, or both, experience pain, stiffness, and physical functional impairment. The Hospital Anxiety and Depression Scale (HADS)[30] is a 14-item Likert scale that assesses symptoms of depression (7-item subscale) and anxiety (7-item subscale). Both questionnaires were administered at baseline, postoperative day (POD) 4, 6 weeks, and 3 months after THA. When administered on POD 4, patients were asked to report how they had been feeling while in hospital.

Functional outcomes

The timed get-up-and-go test, the stair test, and the 6 min walk test were used to evaluate functional performance.

Timed get-up-and-go test

Patients were asked to stand up from a standard arm chair,[31 32] walk at a safe and comfortable pace for 3 m, and then return to a sitting position in the chair. The 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 before surgery and 6 weeks and 3 months after surgery. An important within-patient change has been estimated to be ~2.5 s.[33 34]

Stair test

Patients were asked to ascend and descend one flight of nine stairs in their usual manner, at a safe and comfortable pace.[35 36] Test completion, length of time to complete the test, aids used (crutches, cane, railing), ascending and descending pattern, and pain intensity at the site of surgery were recorded. This test was administered before surgery and 6 weeks and 3 months after surgery. An important within-patient change has been estimated to be ~5.5 s.[33 34]

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.[37–39] Standardized encouragement was offered to all patients every 60 s, because research has shown that encouragement improves performance.[40] Total distance walked, test completion, and pain intensity at the site of surgery were recorded. This test was administered before surgery and at 6 weeks and 3 months after surgery. An important within-patient change has been estimated to be ~62 m.[33 34]

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[41] have suggested that for self-report measures an important between-group difference is less than an important within-patient change. Applying this principle to the WOMAC physical function scale, we specified an important between-group difference to be approximately 5 points at 6 weeks and 4 points at 3 months postarthroplasty. The power was set at 0.80, and the overall type I error probability at 0.05, corrected to 0.0167 because of comparisons at three time points (baseline, 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 timed get-up-and-go test, the stair test, and the 6 min walk test between the groups. Dependent variables were the outcome measures assessed at multiple time points (i.e. timed get-up-and-go test, stair test, and 6 min walk test). The independent variable was treatment group (pregabalin or placebo), and the covariates were gender, age, and the before-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 February 2009 and July 2012. The CONSORT[42] flow chart outlining the recruitment and retention of study patients is shown in Figure 1. Overall, 380 patients were approached for participation, 173 patients declined participation, and 207 patients consented to participate in the study, 23 of whom were ineligible to participate before randomization as a result of inappropriate blood work (i.e. creatinine >104). Of the 184 patients randomly assigned to receive pregabalin or placebo, 162 patients remained in the study on POD 4; 77 of 92 patients (83%) remained in the placebo group, and 85 of 92 (92%) patients remained in the control group on POD 4. The reasons for withdrawal or dropout in the placebo group before POD 4 were as follows: eight patients were removed because of severe adverse effects (one patient because of severe pain, five patients because of nausea and vomiting, of whom one had concomitant headaches, and two patients cited severe dizziness), one patient was a screen failure (missed creatinine >104 μmol/L) and ingested the initial study medications, one patient sustained a femoral fracture on the morning of POD 4, two patients received a general anaesthetic, one patient refused to take the study medications on POD 1, one patient was removed prematurely because of an i.v. PCA switch, and one was removed by the attending surgeon because of a low haemoglobin count. The reasons for withdrawal or dropout in the pregabalin group before POD 4 were as follows: four patients were removed because of severe adverse effects (one patient had a vasovagal episode on POD 2, two patients had severe dizziness, and one patient had dizziness and visual disturbances), one patient was given a general anaesthetic, one patient was removed by their attending physician because of a low blood pressure and heart rate, and one patient refused to take the study medications on POD 2. Three months after surgery, 130 patients remained in the study; 60 patients in the placebo group (17 patients were lost to follow-up), and 70 patients in the pregabalin group (15 patients were lost to follow-up).

Baseline patient characteristics and clinical variables

There were no significant differences in age, sex, ASA class, BMI, or any of the psychological and functional measures between patients in the placebo and pregabalin groups (Table 1).

Performance and patient-report measures; primary outcomes

Results of the performance outcome measures (timed get-up-and-go test, stair test, 6 min walk test, and WOMAC function) and pain scores across groups at baseline, 6 weeks, and 3 months are presented in Tables 2 and 3. There were no statistically significant differences between the pregabalin and placebo groups for any of the performance outcome measures. Furthermore, there were no clinically significant between-group differences in physical functioning scores (difference of 5 points on the WOMAC physical functioning subscale) at 6 weeks and 3 months.

Secondary outcomes

Opioid consumption

Cumulative morphine consumption was significantly lower at 12, 18, and 24 h after surgery between the pregabalin and placebo groups ($P<0.05$; see Fig. 2).

Pain in hospital

There were no significant differences in pain intensity scores at rest or with movement when assessed three times a day until POD 4.

Adverse effects

There was a higher incidence of nausea 12 h after THA and of pruritus on POD 1 in the placebo (10% for both nausea and pruritus) compared with the pregabalin group (5%; 3.5%, respectively); ($P=0.019$; $P=0.019$, respectively) and of vomiting in the pregabalin group (2%) compared with the placebo group (0%) 1 day after THA ($P=0.015$). There were no other differences at any point during hospital stay with respect to nausea, pruritus, vomiting, sedation, dizziness, or visual disturbances.

One week postdischarge pain diary outcomes

The NRS pain intensity scores were significantly lower in the pregabalin group compared with the placebo group on the first 7 days after hospital discharge ($P<0.05$; see Fig. 3).

Adjunctive opioid consumption (Percocet and Tylenol 3) was also significantly lower in the pregabalin group compared with the placebo group during the first 7 days after hospital discharge ($P<0.05$).

Hospital anxiety and depression scores on postoperative day 4 and at 6 weeks and 3 months

There were no significant differences in HADS anxiety scores at baseline, POD 4, 6 weeks, or 3 months between pregabalin and placebo groups. The HADS depression score was significantly

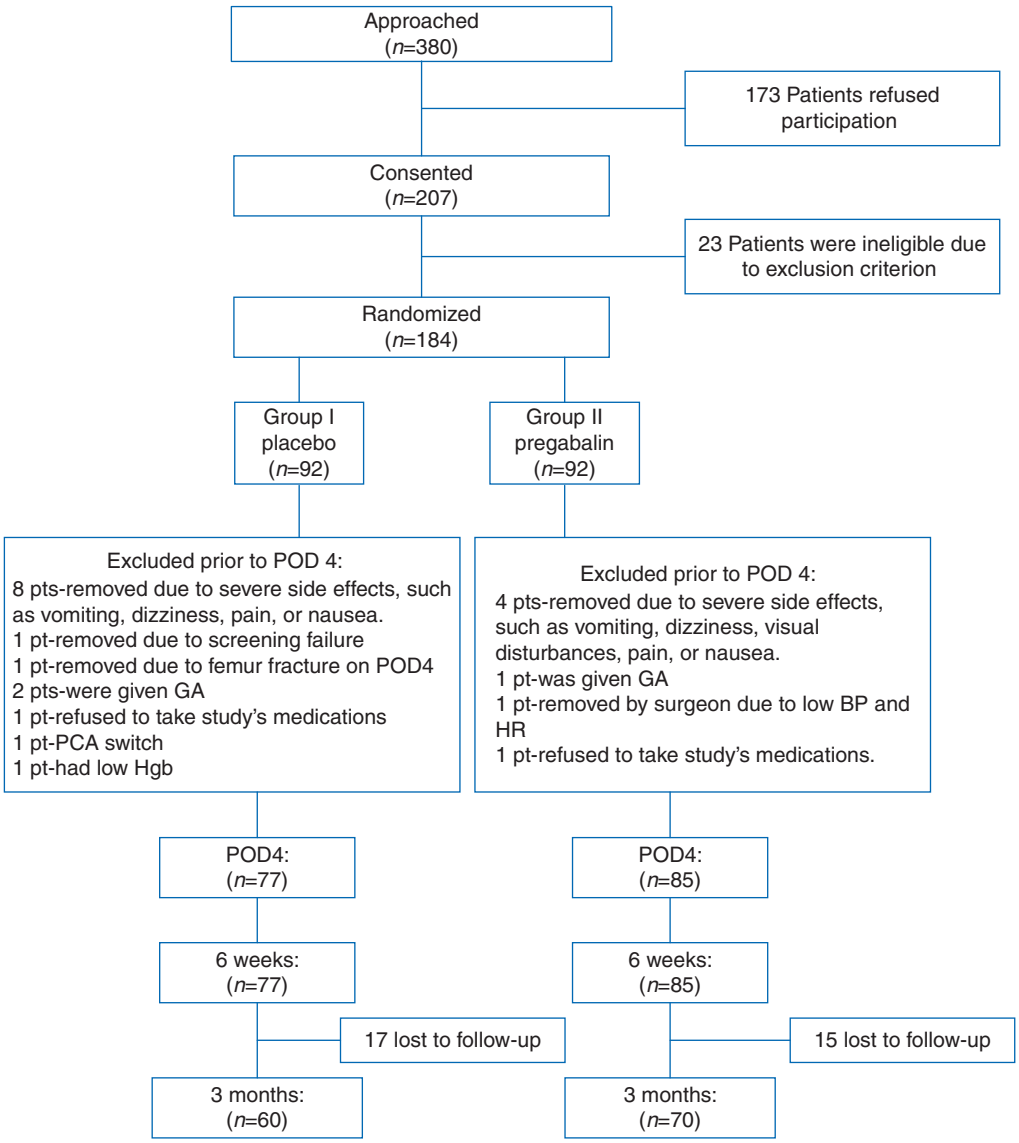

Fig 1 Patient enrolment and study flow. BP, blood pressure; GA, general anaesthesia; Hgb, haemoglobin; HR, heart rate; PCA, patient-controlled analgesia; POD 4, postoperative day 4; pt, patient.

lower in the pregabalin group [3.9 (3.1)] compared with the placebo group [5.0 (3.8)] on POD 4 (P=0.048). There were no significant differences in depression scores at baseline, 6 weeks, or 3 months after THA.

Discussion

Pregabalin has been found to reduce pain and opioid consumption when given as an adjunct for surgeries in which general anaesthesia is used as the primary anaesthetic modality.[43 44] The present study was designed with the primary aim of examining whether the addition of pregabalin to a perioperative THA analgesic regimen (which includes spinal anaesthesia and perioperative celecoxib) while in hospital and for 1 week postdischarge improves pain and functional outcomes up to 3 months after surgery. The present study did not find significant differences between pregabalin and placebo groups in the primary measures of function (both physical and patient reported) at 6 weeks or 3 months after THA (Table 2). Furthermore, pain scores did not differ between groups with respect to each performance-based measure (Table 3). This study found that patients who received pregabalin used significantly less i.v. PCA morphine in the first 24 h after surgery (Fig. 2). This finding is consistent with results from a meta-analysis examining pregabalin after gynaecological surgery.[45] Furthermore, a recent meta-analysis that pooled data from 24 trials supports the finding that perioperative pregabalin results in a 16% reduction in analgesic consumption in surgeries associated with pronociceptive pain (e.g. spine, joint arthroplasty, and amputations).[46] The present results do not support the hypothesis of superior functional performance long term in the pregabalin *vs* the placebo group.

There continues to be a significant gap in the care of patients after discharge from hospital.[47] Often, patients are sent home after surgery without multimodal analgesic regimens that are similar to hospital-based regimens. Most commonly, patients are prescribed a single opioid-based medication.[48] Therefore, patients unable to tolerate opioid-based medications are left to struggle with moderate-to-severe postoperative pain. We designed this trial to assess the postdischarge time period and the pain relief afforded to patients during the first week after hospital discharge while the study medications were continued. The results showed that patients receiving pregabalin daily for 1 week after hospital discharge had lower numerical rating scores every day that the pain was assessed when compared with patients who were given placebo (Fig. 3). Patients in the pregabalin group also used less adjunctive opioid-based medications (Percocet, Tylenol 3) during the 1 week after discharge ($P<0.05$).

Table 1 Patient characteristics and baseline self-report characteristics. All data are presented as the mean (SD) except sex and ASA class, which are frequency. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Characteristic	Placebo group	Pregabalin group
Age (yr)	60.1 (8.8)	60.2 (9.5)
Sex (male/female)	41/38	41/42
BMI (kg m^{-2})	28.7 (4.3)	29.1 (6.9)
ASA class		
I	4	8
II	20	25
III	0	2
WOMAC pain (0–10)	9.0 (3.4)	9.6 (3.5)
WOMAC stiffness (0–8)	4.3 (1.7)	4.4 (1.6)
WOMAC physical function (0–68)	32.8 (10.1)	34.9 (11.8)

Inadequately managed acute pain is a key factor in poor functioning after surgery,[49] and while postdischarge monitoring of pain remains under-reported there is evidence to suggest that the management of acute pain after surgery is suboptimal, with pain intensifying after discharge from hospital.[4] A recent systematic review of persistent neuropathic pain after surgery has identified that persistent neuropathic pain is a long-term problem for 6% of patients after hip and knee arthroplasty.[50] At the present time, there is a paucity of literature regarding safe and effective management of postoperative pain as patients transition from the hospital to home and community. Our results demonstrate that administeration of pregabalin during the first 7 days after hospital discharge reduced pain intensity (Fig. 3) and the need for supplemental opioid analgesic medication and is safe. The addition of the anticonvulsant medications (i.e. gabapentin and pregabalin, $\alpha_2\delta$ subunit voltage-dependent calcium channel blockers) may prove to be a useful tool in the postdischarge time period with patients struggling from prolonged moderate-to-severe acute postsurgical pain.[51] In a recent systematic review, even though results between the studies included were heterogeneous at 3 month follow-up, pregabalin was proposed to have an effect with respect to modifying postsurgical pain trajectories and reducing the development of chronic postsurgical pain.[52] However, in light of a recent publication demonstrating that several cohorts of patients did not experience the preventive effect for pregabalin on chronic post surgical pain (CPSP)[53] and the evidence we present herein, this conclusion needs to be reassessed.

Patients receiving pregabalin had lower in-hospital depression scores on POD 4 compared with placebo-treated patients. However self-report measures of anxiety, depressive symptoms, and pain disability at all other time points throughout the trial were unaffected by pregabalin administration. There was a reduction in pain disability index scores from baseline to 3 months in both groups, which demonstrates the effectiveness of THA in

Table 2 Performance and patient-reported physical function measures. *Negative difference favours pregabalin group. †Positive difference favours pregabalin group. The timed up-and-go and stair tests are scored based on the number of seconds associated with completing the task. The 6 min walk test is scored as the distance covered (in metres). The WOMAC total scores range from 0 to 68 for the physical function subscale, with higher scores indicating worse pain, stiffness, or physical limitations. Postoperative day 4 data are not reported here because a significant proportion of patients were unable to complete functional outcome measures at this time point. CI, confidence interval; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Test	Placebo group		Pregabalin group		Adjusted difference (95% CI)
	n	Unadjusted mean (SEM)	*n*	Unadjusted mean (SEM)	
Timed up-and-go (s)*					
Before surgery	78	12.6 (0.5)	83	13.1 (0.7)	0.6 (−1.0, 2.2)
6 weeks	67	10.8 (0.4)	81	11.5 (0.5)	0.8 (−0.8, 2.5)
3 months	54	9.1 (0.4)	66	9.2 (0.4)	0.1 (−1.7, 2.0)
Stair test (s)*					
Before surgery	78	18.9 (1.4	84	18.9 (1.0)	−0.2 (−3.5, 3.2)
6 weeks	67	19.2 (1.3)	78	19.6 (1.3)	0.4 (−3.21, 3.9)
3 months	54	12.2 (0.5)	66	12.3 (0.7)	−0.2 (−4.1, 3.6)
6 min walk (m)†					
Before surgery	71	376 (14)	76	366 (14)	−10 (−49, 28)
6 weeks	64	394 (12)	80	392 (11)	−4 (−43, 35)
3 months	52	476 (11)	66	475 (12)	2 (−45, 40)
WOMAC function (0–68)*					
Before surgery	77	32.8 (1.2)	83	34.9 (1.3)	2.2 (−1.4, 5.9)
6 weeks	54	14.4 (1.4)	59	12.4 (1.3)	−1.4 (−5.8, 2.9)
3 months	53	8.0 (1.0)	65	9.0 (1.1)	1.2 (−3.0, 5.5)

Table 3 Pain ratings. Pain scores for the timed up-and-go, stair test, and 6 min walk test are based on an 11-point numerical rating scale for pain (0='no pain' and 10='worst pain possible pain'). The WOMAC pain score ranges from 0 to 20 for the pain subscale

Test	Placebo group		Pregabalin group	
	n	Median (first, third quartiles)	*n*	Median (first, third quartiles)
Timed up-and-go (/10)				
Before surgery	79	4 (2, 6)	83	5 (3, 7)
6 weeks	69	0 (0, 1)	82	0 (0, 1)
3 months	54	0 (0, 0)	65	0 (0, 0)
Stair test (/10)				
Before surgery	77	2 (4, 6)	83	5, (2, 7)
6 weeks	68	0 (0, 2)	81	0 (0, 1)
3 months	54	0 (0, 1)	65	0 (0, 1)
6 min walk (/10)				
Before surgery	75	5 (3, 7)	80	5 (3, 7)
6 weeks	67	1 (0, 2)	82	1 (0, 2)
3 months	53	0 (0, 1)	65	0 (0, 1)
WOMAC pain (/20)				
Before surgery	79	9 (7, 12)	83	10 (8,12)
6 weeks	75	3 (1, 5)	82	2 (1, 4)
3 months	53	1 (0, 3)	69	1 (0, 3)

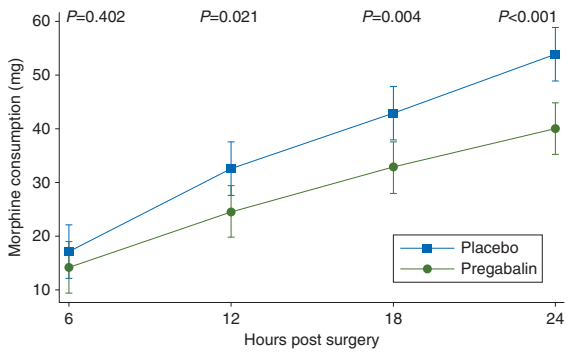

Fig 2 Cumulative morphine consumption during 24 h [mean (95% confidence interval)].

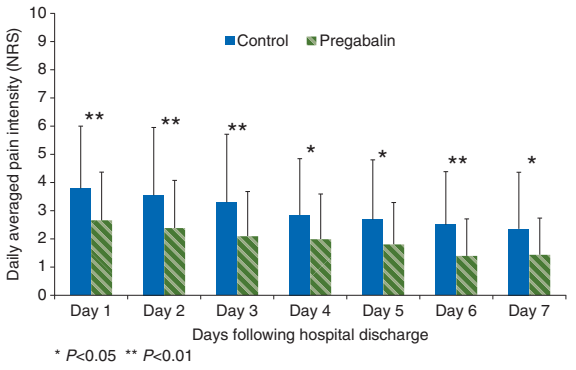

Fig 3 Daily pain scores 1 week after discharge from hospital. NRS, numerical rating scale.

reducing pain disability. Studies have shown that high levels of preoperative pain and anxiety are independent risk factors for acute postsurgical pain[54] and are associated with the development of chronic postsurgical pain after knee arthroplasty surgery.[55] Our group also demonstrated that gabapentin 1200 mg, when administered to highly anxious females (i.e. baseline anxiety >5/10) undergoing major surgery, significantly reduced preoperative anxiety and pain catastrophizing before major surgery.[56] A recent systematic review has also found that pain catastrophizing predicts CPSP after total knee arthroplasty.[57] This emerging literature suggests that patients should be screened before surgery for psychological vulnerabilities, and based on the results, psychological interventions, in addition to multimodal preventive analgesic strategies such as the ones implemented in this trial, should become a mainstay for perioperative postsurgical care.[51]

This is the first study to compare the efficacy of pregabalin *vs* placebo for recovery of physical function at three time points (baseline, 6 weeks, and 3 months) for patients undergoing total hip arthroplasty. Although negative for such outcomes, a reduction in cumulative 24 h opioid consumption and superior pain relief for 1 week postdischarge was evident. The present results are specific to our multimodal analgesic regimen (i.e. spinal anaesthesia and celecoxib) and cannot be generalized to the same surgery with alternative perioperative pain regimens or other surgeries performed under general anaesthesia. The major limitation to the present study is the dropout rate at the 3 month time point. We examined baseline differences between patients who did *vs* did not complete the 3 month follow-up. The results showed no significant differences between completers *vs* non-completers in terms of baseline functional outcomes, pain, depression, anxiety, and pain interference (*P*-values >0.05). Given that there was no difference in physical function or pain at 6 weeks post-THA, it is unlikely that this would have been different at 3 months.

In conclusion, an in-hospital regimen of pregabalin (150 mg before surgery followed by 75 mg BID), co-administered with celecoxib, decreased immediate postoperative analgesic requirements. Patients discharged with pregabalin (75 mg BID) for 1

week after surgery had better pain control while at home and a reduced need for supplemental opioid medications. The pregabalin regimen did not improve pain or physical function 6 weeks or 3 months after surgery. Specific subpopulations of patients, excluded from the present study, may have had significant benefits from the opioid-sparing effects of pregabalin in the perioperative period. Future studies should focus on the efficacy of perioperative pregabalin for patients with obstructive sleep apnoea or chronic pain and those taking opioid medications, because these subpopulations might benefit even more with respect to the pregabalin-induced opioid-sparing effect and the reduction in postdischarge pain we observed in the present study.

Authors' contributions

Study design: H.C., J.A., D.K., J.G., J. Kay, J. Katz.
Overseeing the study at the Holland Centre: C.M., I.T.A.
Data collection: J.A.
Data analysis: G.P., P.S., J. Kay.
Review of data analysis: H.C.
Writing the manuscript: H.C., G.P., C.M., A.H., D.K., I.T.A., J. Kay, J. Katz.
Approval of final manuscript: H.C., G.P., C.M., A.H., P.S., J.A., D.K., I.T.A., J.G., J. Kay, J. Katz.

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Declaration of interest

None declared.

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