Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial

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BACKGROUND: Despite the enormous success of total knee arthroplasty (TKA), chronic neuropathic pain can develop postoperatively and is both distressing and difficult to treat once established. We hypothesized that perioperative treatment with pregabalin, a chronic pain medication, would reduce the incidence of postsurgical neuropathic pain.

METHODS: We performed a randomized, placebo-controlled, double-blind trial of pregabalin (300 mg) administered before TKA and for 14 days after TKA (150–50 mg twice daily). Patients were screened for the presence of neuropathic pain at 3 and 6 mo postoperatively using the Leeds Assessment of Neuropathic Symptoms and Signs scale. Secondary outcomes included postsurgical recovery and rehabilitation measures, including knee range of motion, opioid consumption, postoperative pain scores, sleep disturbance, and time to discharge as well as the occurrence of postoperative systemic complications.

RESULTS: Of the 240 patients randomly assigned to the 2 treatment groups (120 in each), data for the primary outcome were obtained from 113 pregabalin patients and 115 placebo patients. At both 3 and 6 mo postoperatively, the incidence of neuropathic pain was less frequent in the pregabalin group (0%) compared with the placebo group (8.7% and 5.2% at 3 and 6 mo, respectively; \( P < 0.001 \) and \( P = 0.014 \)). Patients receiving pregabalin also consumed less epidural opioids (\( P < 0.003 \)), required less oral opioid pain medication while hospitalized (\( P = 0.005 \)), and had greater active flexion over the first 30 postoperative days (\( P = 0.013 \)). There were no differences in the actual recorded duration of hospitalization between the 2 groups, although time to achieve hospital discharge criteria was longer for placebo patients, 69.0 ± 16.0 h (mean ± sd), than that of pregabalin patients, 60.2 ± 15.8 h (\( P = 0.001 \)). Sedation (\( P = 0.005 \)) and confusion (\( P = 0.013 \)) were more frequent on the day of surgery and postoperative day 1 in patients receiving pregabalin.

CONCLUSION: Perioperative pregabalin administration reduces the incidence of chronic neuropathic pain after TKA, with less opioid consumption and better range of motion during the first 30 days of rehabilitation. However, in the doses tested, it is associated with a higher risk of early postoperative sedation and confusion.

postoperative morphine requirements after total hip arthroplasty,9 and attenuate postoperative pain after laparoscopic cholecystectomy10; however, other studies show no beneficial effect of pregabalin on acute postoperative pain when administered preoperatively for minor gynecological surgery,11 elective ambulatory and short-stay surgery,12 and laparoscopic cholecystectomy.13 However, no clinical study has yet investigated whether perioperative administration of pregabalin can reduce the incidence of postoperative chronic neuropathic pain. The primary objective of this study was to evaluate whether pregabalin given before and for 14 days after TKA reduces the incidence of neuropathic pain assessed at 6 mo postoperatively. Secondary outcomes assessed include knee range of motion (ROM), acute postoperative opioid requirements, and time until hospital discharge criteria is achieved.

METHODS

After receiving IRB approval, from August 2006 to August 2007, 350 consecutive patients scheduled to undergo elective primary TKA were contacted and assessed for study eligibility (Fig. 1). Written informed consent was obtained from each patient. Two hundred forty patients undergoing primary TKA were enrolled in this randomized, placebo-controlled, double-blind trial. Patients were randomized to a treatment group using a computer-generated randomization sequence. This study was approved for a physician-sponsored investigational new drug (IND) No. 72,121 issued (January 2006) by the Food and Drug Administration (FDA).

Inclusion/Exclusion Criteria

Patients were eligible for the study if they were scheduled to undergo a primary TKA with a diagnosis of osteoarthritis of the operative knee and had the ability to understand and read English. Patients were excluded if they were younger than 21 yr or older than 80 yr; had an ASA physical status of IV; had prior use of gabapentin (or pregabalin) or nonsteroidal antiinflammatory drugs (NSAIDs) within 2 wk before surgery; had a history of neuropathic pain or any other chronic pain condition, other than osteoarthritis pain; were pregnant; had a sulfa allergy; or were currently enrolled in another investigational study.

Treatment Protocol

Patients were randomly assigned (SAS Statistical Software 9.1.3) to receive either the study medication or placebo. There was no dose administered on the days before surgery. Patients randomized to the experimental arm of the study received pregabalin 300 mg orally (per os [PO]), 1–2 h before surgery, 150 mg twice daily for the first 10 postoperative days, 75 mg twice daily on Days 11 and 12, and 50 mg twice daily on Days 13 and 14. Pregabalin is not approved by the FDA for perioperative use, and therefore, the primary investigator consulted with the FDA before commencing the study. Dosing was approved in the physician-sponsored IND No. 72,121 by the FDA. Although this is an off-label use of the study drug, the doses do not exceed the daily limit allowed for the treatment of chronic pain. Control patients received PO-matched placebo tablets, at identical time points, with both pregabalin and placebo capsules provided by Pfizer (New York, NY). After discharge, patients were provided with diaries in which they recorded the exact times at which they took pregabalin/placebo each day. All patients were contacted 1 wk after their discharge via a phone call to ensure their compliance with the study.
medication. They were asked to return any unused drug, along with the diaries, at their 1-mo visit to the surgeon’s office. The physicians and nurses managing the patient perioperatively, the personnel involved with postoperative pain assessments and management of the epidural infusion, physical therapists, and the study patients were blinded to group assignments. During the study, only the dispensing pharmacist had knowledge of the study codes. Pfizer, the manufacturer and provider of pregabalin and placebo, was not involved in protocol development, data collection and management, statistical analysis, or manuscript preparation.

In the operating room, patients were sedated with midazolam, and a combined spinal-epidural anesthetic was used for the operation as previously described. After obtaining clear cerebrospinal fluid, 1.5 mL of 0.75% hyperbaric bupivacaine with 25 μg of fentanyl was injected. After the intrathecal injection, a catheter was inserted for epidural drug administration. Patients were sedated with IV propofol for the duration of the surgery. At the completion of surgery, an epidural infusion of fentanyl (5 μg/mL) and bupivacaine (1 mg/mL) was initiated using a continuous basal infusion of 6 mL/h with superimposed patient-controlled epidural analgesia (PCEA) bolus doses. Patients were instructed before surgery to use the PCEA mode, so as to maintain their pain score (at rest) between 2 and 4 on the 11-point numerical rating scale (NRS), where 0 = no pain and 10 = worst possible pain. If the pain scores could not be maintained (NRS ≥4 and the maximum number of PCEA boluses was used), the basal infusion rate was increased while maintaining the PCEA mode. However, the maximum amount of epidural solution that could be used per hour was 10 mL. The epidural infusion was discontinued between 32 and 42 h postoperatively. Patients were then transitioned to oral opioid medications (morphine, oxycodone, and hydromorphone) as needed for adequate pain control (NRS <4). All patients received preoperative celecoxib 400 mg orally, 1–2 h before surgery and 200 mg PO twice daily for 3 days while in the hospital, to conform to the multimodal analgesia protocol used at our facility.

Surgery
Prophylactic antibiotics (cefazolin IV or vancomycin IV) were administered to all patients before the skin incision. TKA was performed under tourniquet control, using an abbreviated medial parapatellar approach with the arthrotomy extending into the quadriceps tendon for 2–4 cm above the superior pole of the patella, and without patellar eversion. A primary, cruciate retaining TKA was performed in all cases (NexGen CR, Zimmer, Warsaw, IN); all components were cemented, and the patella was resurfaced in all cases. At the time of capsular closure, 60 mL of 0.25% bupivacaine with epinephrine was infiltrated into the wound. The knee was closed in 90° of flexion over a nonreinfusion drain (Hemovac, Zimmer Snyder, Warsaw, IN). The drain was discontinued on postoperative day 1, and patients were started on a physical therapy program that included weight bearing as tolerated and ROM exercises as guided by a physical therapist.

Outcome Measures
Adverse Events
Based on the package labeling for pregabalin, the occurrence of sedation, confusion, dizziness, headache, dry mouth, peripheral edema, and diplopia were assessed daily during hospitalization. In addition, occurrences of postoperative nausea and vomiting and pruritus were recorded based on answers to standardized questions in the morning and evening each day during hospitalization. Patients with postoperative nausea and vomiting were treated with metamizolamine (10 mg) or ondansetron (4 mg) if needed. Adverse events data after hospitalization were supplemented by the surgeon’s clinical records up to the 6-mo patient visit.

Chronic Neuropathic Pain and Related Outcomes
Patients were evaluated in a blinded fashion for lower extremity neuropathic pain at 3 and 6 mo after TKA using a measure administered during a telephone interview. The 3- to 6-mo time points are often used to define when acute postsurgical pain becomes chronic pain. During this time period, there were no restrictions on patients’ use of analgesic drugs. Clinical symptoms of neuropathic pain were assessed, using the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS), to determine the presence of neuropathic pain in the operated leg at each time point (3 and 6 mo postoperatively). S-LANSS is a validated, weighted 7-item assessment tool for neuropathic pain (yes or no for each pain measure) with a maximum score of 24. An S-LANSS score of 12 or more was an indication of chronic neuropathic pain. The 7 variables included 2 self-examination items: allodynia (assessed by gentle rubbing of the operated leg) and hyperalgesia (gently applied pressure from the fingertip); and 5 pain symptoms: pins and needles, skin color change, sensitivity to touch, sudden bursts of pain, and burning. Patients with an S-LANSS score of 12 or more at 6 mo came to the physician’s office for a standardized physical examination, which included the S-LANSS examination items (allodynia and hyperalgesia) directly assessed by the physician, plus a pinprick evaluation (physician applying pin to painful area and comparing it to a nonpainful area and recording an increased response in the painful area versus control area). Presurgery NRS scores were obtained from the orthopedic presurgery office visit. To account for concomitant analgesic use in the 6-mo postsurgery period, we reviewed the records of patients from postsurgery orthopedic office visits, up to 6 mo.

In addition, for those patients who were identified with neuropathic pain of the operative knee at 6 mo, knee function was quantified using the validated Knee
injury and Osteoarthritis Outcome Score–Physical function Short-form (KOOS-PS).\textsuperscript{17} Comparisons of knee function were made between patients with chronic postoperative neuropathic knee pain, case matched by age and surgeon, with 2 sets of patients without chronic pain, 1 from the pregabalin and the other from the placebo groups, using a random selection. Using the KOOS-PS, patients ranked each of the following 7 variables as to the degree of difficulty, from none to extreme (point values: 0–4): rising from bed; putting on socks/stockings; rising from sitting; bending to the floor; twisting/pivoting on the affected knee; kneeling; and squatting. The raw summed score from the KOOS-PS was then converted to a 0–100 scale, Rasch-based person score.\textsuperscript{17}

**Range of Motion**

The degree of active (patient moving the knee) and passive (movement of the knee with the aid of a physical therapist) knee flexion, measured using a goniometer,\textsuperscript{14,18} tolerated by the patient on postoperative days 1–3 was recorded by the physical therapist twice daily, and the maximum daily measure was used for analysis. Follow-up active ROM was assessed at 1 mo postoperatively by orthopedic nurses blinded to the study codes.

**Epidural Drug Use and Postoperative Pain Assessment**

Epidural medication consumption was recorded for each 4-h interval from the completion of surgery to the time that the epidural was discontinued (same as the time to achieve hospital discharge criteria). Because the discontinuation time varied from patient to patient (as they achieved physical therapy criteria), the average hourly consumption (total analgesic used divided by the total infusion time) was used as the measure of epidural drug use. Pain scores at rest were assessed with the NRS rating every 8 h during the immediate postoperative phase (the first 32–42 h after surgery). All other oral opioid consumption during the entire postoperative phase (the first 32–42 h after surgery). Pain scores at rest were assessed by the total infusion time) was used as the measure of epidural analgesic consumption rate, supplemental postoperative opioid use, KOOS-SP knee score, and time for patients to achieve hospital discharge criteria were compared between the 2 groups using the 2-sample Student’s \( t \)-test. All repeated measurement outcomes (active ROM, passive ROM, and sleep interference) were analyzed with a mixed procedure repeated-measures model with an autoregressive covariance structure, estimated using the maximum likelihood method. NRS pain scores over a postoperative period up to 42 h were analyzed, after verifying that <20% of the scores were 0, as a repeated measurement outcome and evaluating the distributional assumptions. Although the mixed models used are robust against violations of nonnormality, when distributional violations were identified, nonparametric methods were used to confirm parametric results. The incidence of neuropathic pain (S-LANSS \( \geq 12 \)), allodynia, or hyperalgesia at 3 and 6 mo, and adverse events were analyzed by \( \chi^2 \) test and confirmed with exact methods.

**RESULTS**

Two hundred forty patients were randomly assigned to the 2 treatment groups, with 120 per group (Fig. 1). All patients received the preoperative dose, pregabalin or placebo, and all patients were therefore included in the...
Table 1. Patient Demographics and Surgical Data

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin (N = 120)</th>
<th>Placebo (N = 120)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.0 (8.3)</td>
<td>63.3 (8.9)</td>
<td>0.579</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>34.2 (8.4)</td>
<td>34.6 (7.7)</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Gender (counts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>91 (76%)</td>
<td>84 (70%)</td>
<td>0.309a</td>
</tr>
<tr>
<td>Male</td>
<td>29 (24%)</td>
<td>36 (30%)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>104 (24)</td>
<td>101 (23)</td>
<td>0.384</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>82 (33)</td>
<td>81 (34)</td>
<td>0.595</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>160 (135)</td>
<td>201 (160)</td>
<td>0.065</td>
</tr>
<tr>
<td>Total crystalloid (mL)</td>
<td>2320 (625)</td>
<td>2471 (697)</td>
<td>0.123</td>
</tr>
</tbody>
</table>

There were no significant differences between the treatment groups.

a χ² test.

intent-to-treat analysis for the secondary end points of the study. An intent-to-treat analysis for the primary outcome (at 6 mo) was performed on 113 and 115 patients, respectively, for the pregabalin and placebo groups. In the pregabalin and placebo groups, 7 and 5 patients, respectively, were lost to follow-up (Fig. 1).

Nine patients in the pregabalin group and 2 patients in the placebo group did not receive any postoperative study medication. These 11 patients were included in the intent-to-treat analysis for both the primary and secondary end points, where there were data, because a single preoperative dose alone may influence postoperative outcomes. The reasons why the 9 patients in the pregabalin group did not receive any postoperative medication included 4 patients who withdrew consent after the operative procedure (1 secondary to sedation), 3 surgical cancellations (for reasons unrelated to the study protocol), 1 postoperative arrhythmia, and 1 unsuccessful spinal-epidural placement. The reasons for withdrawal in the control group included 1 unsuccessful spinal-epidural placement and 1 patient with severe early postoperative hypotension. Another 4 patients in the pregabalin group and 1 patient in the placebo group received <14 days of postoperative study medication and were also included in the intent-to-treat analysis. Demographic characteristics and intraoperative variables were similar between the 2 treatment groups (Table 1).

Adverse Events

Sedation, confusion, and dry mouth occurred more frequently in the pregabalin group than in the placebo group on the day of surgery and the first postoperative day (Table 2). By postoperative day 2, no adverse event reached statistical significance. There were no falls in this studied population that the investigators observed. No extra physician consults were needed for adverse effects such as sedation. If sedation occurred, we compensated by reducing the basal epidural analgesic flow rate. At the 6-mo postoperative

patient visit, there were no clinically significant adverse events in either group.

Outcome Measures

Chronic Neuropathic Pain and Related Outcomes

The incidence of neuropathic pain at 3 and 6 mo postsurgery was less frequent in the pregabalin group compared with the placebo group. At 3 mo, the incidence of neuropathic pain after TKA was 0% (0 of 113 patients) in the pregabalin group compared with 8.7% (10 of 115) in the placebo group (P = 0.001). The incidence of allodynia in the operated leg was also lower (P = 0.002) at 3 mo for the pregabalin group (2%, 2 of 113) than for the placebo group (12%, 14 of 115); the incidence of hyperalgesia in the operated leg was lower (P = 0.009) at 3 mo for the pregabalin group (8%, 8 of 113) than for the placebo group (20%, 23 of 115). At 6 mo postoperatively, the incidence of neuropathic pain was 0% (0 of 113) in the pregabalin group and 5.2% (6 of 115) in the placebo group (P = 0.014). The incidence of allodynia in the operated leg was also lower (P = 0.002) at 6 mo for the pregabalin group (0%, 0 of 113) than for the placebo group (8%, 9 of 115); the incidence of hyperalgesia in the operated leg was lower (P = 0.006) at 6 mo for the pregabalin group (2%, 2 of 113) than for the placebo group (11%, 12 of 115). The neuropathic pain in all 6 patients with an S-LANSS score of 12 or more at 6 mo was confirmed by physical examination by the physician. All 6 patients had allodynia and hyperalgesia to touch, and 5 of 6 had abnormal response to pinprick. There was no difference in preoperative pain scores (P = 0.343) between the pregabalin group (NRS = 7.7 ± 1.9, n = 67) and the placebo group (NRS = 8.0 ± 1.3, n = 66). As for concomitant analgesic use, 32 of 240 patients used NSAIDs during this 6-mo postoperative period, 16 in the pregabalin group and 16 in the placebo group (P = 1.000). Twenty-four of 240 patients used opioids during this postoperative period, 15 in the pregabalin group and 9 in the placebo group (P = 0.282). Eight of 240 patients used gabapentin or pregabalin during this postoperative period, 0 in the pregabalin group and 8 in the placebo group (P = 0.007). Twenty-four of 240 patients used acetaminophen/tramadol during this postoperative period, 11 in the pregabalin group and 13 in the placebo group (P = 0.830).

The KOOS-PS knee function score (0–100) for patients with chronic pain at 6 mo (all 6 in placebo group) was increased, 49.0 ± 16.2, compared with 6 age-matched pregabalin patients, 12.4 ± 5.5 (P = 0.003), and also compared with 6 age-matched placebo nonchronic pain patients, 25.7 ± 7.2 (P = 0.012).

Range of Motion

Patients in the pregabalin group had greater active flexion of the operated knee during postoperative days 1–30 compared with placebo patients (mixed model: fixed effect, F = 6.23, P = 0.013), and change over time was highly significant (P < 0.0001) (Fig. 2).
Passive ROM during postoperative days 1–3 was also improved in the pregabalin group compared with the placebo group (mixed model: fixed effect, $F_{11005} = 4.41$, $P = 0.037$), and change over time was highly significant ($P = 0.0013$). Passive ROM on Day 2 was 88.9° ± 9.9° in pregabalin patients compared with 83.7° ± 15.2° in placebo patients ($P = 0.012$).

**Epidural Drug Use and Pain Assessment**
In the immediate postoperative period, epidural drug consumption was less in the pregabalin group (5.77 ± 1.31 mL/h) than in the placebo group (6.40 ± 1.26 mL/h; $P = 0.003$). In addition, the number of epidural PCEA boluses delivered was less in the pregabalin group (0.36/h [0.21–0.55], median [interquartile range]) than in the placebo group (0.63/h [0.30–0.98]) ($P = 0.009$). However, the frequency of a PCEA bolus is a difficult assessment of pain because a patient taking pregabalin who is sedated will likely not push the button for a bolus. In accordance with the study protocol, the NRS values at rest, during the immediate postoperative phase, did not differ between treatment groups (mixed model: fixed effect, $F = 2.77$, $P = 0.098$; and no change

![Figure 2. Active range of motion (ROM) of operated knee over postoperative days 1–30 showing greater flexion in the pregabalin group. Data plotted as mean ± se.](image)

### Table 2. Incidence of Adverse Events on Day of Surgery (Day 0), Postoperative Days 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregabalin</td>
<td>Placebo</td>
<td>Pregabalin</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>$n = 120$</td>
<td>$n = 120$</td>
<td>$n = 106$</td>
</tr>
<tr>
<td><strong>Sedation</strong></td>
<td>16 (13%)</td>
<td>4 (3%)</td>
<td>28 (26%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.005*</td>
<td></td>
<td>0.019*</td>
</tr>
<tr>
<td><strong>Confusion</strong></td>
<td>6 (5%)</td>
<td>0 (0%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.013*</td>
<td></td>
<td>0.011*</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>18 (17%)</td>
</tr>
<tr>
<td>$P$</td>
<td>1.00</td>
<td>0.197</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.316</td>
<td></td>
<td>0.076</td>
</tr>
<tr>
<td><strong>Dry mouth</strong></td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.081</td>
<td></td>
<td>0.027*</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>9 (8%)</td>
<td>10 (8%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.811</td>
<td></td>
<td>0.642</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>$P$</td>
<td>1.00</td>
<td></td>
<td>0.479</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>1 (1%)</td>
<td>6 (5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.055</td>
<td></td>
<td>0.262</td>
</tr>
<tr>
<td><strong>Peripheral edema</strong></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>$P$</td>
<td>1.00</td>
<td></td>
<td>0.316</td>
</tr>
<tr>
<td><strong>Diplopia</strong></td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>$P$</td>
<td>0.316</td>
<td></td>
<td>0.323</td>
</tr>
</tbody>
</table>

* There was a statistically significant difference ($P < 0.05$) between groups.
over time \( [F = 2.14, P = 0.0750] \). This is consistent with the instruction given to the study patients to maintain their pain score between 2 and 4 using PCEA bolus doses. However, the NRS values tended to be lower with pregabalin than with placebo at the discharge physical therapy session, during both active ROM \((5.2 \pm 2.4 \text{ vs } 6.1 \pm 2.4; P = 0.059)\) and passive ROM \((6.0 \pm 2.3 \text{ vs } 7.0 \pm 2.2; P = 0.032)\) testing. Supplemental postoperative oral opioid use (in morphine equivalents) to control pain over the entire hospital stay was less in the pregabalin group, 4.55 mg \((2.40–9.16)\), compared with the placebo group, 7.32 mg \((4.32–10.70; P = 0.005)\). The dosage of metoclopramide and ondansetron used postoperatively by the patients with neuropathic pain at 6 mo (all in the placebo group) versus those without pain (all remaining patients combined) did not differ for either metoclopramide \((P = 0.8099)\) or ondansetron \((P = 0.4374)\).

### Time to Meeting Hospital Discharge Criteria

Patients who were in the pregabalin group met hospital discharge criteria faster than patients in the control group (mean \(60.2 \pm 15.8 \text{ h}\) compared with \(69.0 \pm 16.0 \text{ h}\), respectively; \(P = 0.001)\). The actual hospital discharge time, however, was not different between the 2 groups (mean time to discharge with pregabalin was \(72.1 \pm 18.8 \text{ h}\) compared with \(73.2 \pm 15.6 \text{ h}\) with placebo; \(P = 0.702)\).

### Sleep Disturbance

The pregabalin patients had less sleep interference compared with placebo patients (mixed model: fixed effect, \(F = 4.50, P = 0.038)\), and change over time was highly significant \((P < 0.0001)\) while in the hospital. On the first postoperative night, the sleep interference score was \(2.9 \pm 3.3\) for the pregabalin group compared with \(4.6 \pm 3.2\) for the placebo group (stepdown Bonferroni: \(P = 0.035)\). On each succeeding night, there were no statistical differences between groups.

### DISCUSSION

The principal finding from this randomized, placebo-controlled trial of perioperative administration of pregabalin to patients undergoing TKA was a significant decrease in the incidence of chronic neuropathic pain \((0\%\) compared with \(5.2\%\) in the placebo group) at 6 mo after surgery. The reported incidence of chronic neuropathic pain after TKA has varied thresholds (signs and symptoms of neuropathic pain), but \(20\%\) of the patients had moderate chronic pain at \(4\) mo postoperatively.\(^{21}\) The wide variation in prevalence estimates is likely related to retrospective study designs, variable criteria for neuropathic pain, or small sample size.\(^{4}\) Neuropathic pain of the operated knee can result in substantial discomfort and limit activities of daily living. This is the first large prospective clinical trial examining the incidence of chronic neuropathic pain after TKA and defining a strategy to prevent the development of this distressing chronic pain syndrome.

In a similar study, the administration of gabapentin to women undergoing total abdominal hysterectomy did not reduce acute postoperative pain, but there was a decrease in pain at \(1\) mo postoperatively.\(^{22}\) A preoperative dose of \(1200\) mg was chosen for that study, and it was repeated daily for the first \(7\) days postoperatively. In another study of abdominal hysterectomy, gabapentin was given at \(1800\) mg/day starting \(1\) h preoperatively for \(72\) h, but long-term pain was not evaluated.\(^{23}\) Similarly, we designed our study with the intent to prevent spinal cord sensitization by preoperatively administering a recommended upper limit dose \((300\) mg\) of pregabalin that was continued for \(14\) days after surgery \((150\) mg twice daily for \(10\) days and then titrated down for another \(4\) days\). Although we chose a \(14\)-day postoperative regimen, the minimum duration or the dose required to prevent the long-term sequelae of spinal cord sensitization after a major surgery such as TKA cannot be determined from this study.

Chronic neuropathic pain is a complex condition that has a profound effect on both quality of life and expenditures for health care.\(^{24}\) This was evident by the results of our study, demonstrating reduced knee function (higher level of KOOS-PS scores) at \(6\) mo postoperatively in patients with neuropathic pain (in the placebo group of patients) compared with patients without chronic pain. Treatment options for patients who develop neuropathic pain after TKA are challenging and expensive. Patients who undergo repeated TKA for chronic pain of the knee invariably have further exacerbation in knee pain, and in very rare instances, above-knee amputations have been reported.\(^{25}\)

In a large study of \(10,000\) patients with osteoarthritis who underwent TKA, a \(2\)-yr postsurgery survey showed that patients who had persistent pain in the knee had decreased functional improvements.\(^{26}\) Oral perioperative administration of pregabalin improved active and passive ROM after TKA in our study. ROM is an important measure of outcome after TKA.\(^{27}\) It has been demonstrated that 67° of knee flexion is needed for the swing phase of gait, 83° to climb stairs, 90° to descend stairs, and 93° to rise from a chair after TKA.\(^{28}\) Higher degrees of ROM to 106° are required for activities such as shoe tying.\(^{29}\) The active knee flexion (79.5°) attained in our placebo group by Day 3 (typical discharge day) is similar to that reported in other studies using postoperative regional analgesia after TKA.\(^{30,31}\) The pregabalin group, however, demonstrated greater knee functionality (83.9° active flexion = stair climbing) at discharge. It is likely that this beneficial effect on knee function at time of discharge facilitated attainment of nearly full functionality in the pregabalin group (107.0° active flexion = shoe tying)
at 1 mo after surgery, versus 103.4° in the placebo group. These beneficial effects have important economic implications for reducing the costs associated with the additional time in physical therapy necessary to achieve full knee function.32

The beneficial outcomes associated with pregabalin in this study may be related to presurgical administration of a large initial dose and/or a continued large dose for 10 days after TKA. Our first dose at 1–2 h before surgery was not intended to be “preemptive analgesia.” Instead, it was to provide coverage immediately after surgery, when it would have been difficult to administer this oral medication. A recent study with the cyclooxygenase-2 inhibitor celecoxib failed to find a benefit to perioperative administration compared with postoperative administration alone.33 Further studies are needed to assess the benefit, if any, of preoperative administration of pregabalin given the recent studies questioning its analgesic benefit in the early postoperative period and well-documented side effects.11–13,34 It has been suggested that aggressive management of early postoperative pain may reduce the likelihood of long-term pain,35 and this concept has been extended to other surgical procedures that are followed by persistent pain.3 Because our protocol was designed to actively manage acute postoperative pain equally in both the pregabalin and the placebo groups, the reduction in the incidence of long-term postoperative pain after TKA cannot be attributed to amelioration of acute pain. Nevertheless, the ability of pregabalin to reduce short-term central nervous system hypersensitivity in humans36 makes it likely that early and maintained reduction of neuronal excitability by this drug is one possible mechanism for suppression of long-term neuropathic pain. The mechanism of action of pregabalin probably involves binding to voltage-gated calcium channels,37 which are upregulated in the dorsal root ganglia and spinal cord in rat neuropathic pain models.38 The reduction in sleep interference in the pregabalin group may be, in part, attributable to the increased sedation also seen in that group.

There were no statistically significant differences in the actual recorded duration of hospitalization between the 2 groups. With newer treatment strategies for TKA patients, multidisciplinary operational changes are needed to facilitate an earlier discharge from the hospital.39 The 300-mg initial pregabalin dose (before surgery), without the slow dose escalation that is standard practice when pregabalin (or gabapentin) is administered for chronic pain, most likely led to the increased incidence of sedation and confusion in the pregabalin-treated patients during the immediate postoperative period. In a study of pregabalin 100 mg given before minor gynecological surgery, the incidence of lightheadedness, visual disturbance, and difficulty with walking was more frequent with pregabalin than with placebo at 24 h after surgery.11 The 300-mg dose of pregabalin given before surgery produced higher sedation scores at 90 and 120 min after elective ambulatory and short-stay surgery compared with placebo.12 When given to reduce shoulder pain after laparoscopic cholecystectomy, 150 mg of pregabalin given presurgery produced oversedation at the 2-h time point after surgery compared with placebo.13 Therefore, lower pregabalin doses should be considered in future studies to minimize such side effects, and hopefully, maintaining therapeutic efficacy. One of the limitations of this study is the absence of dose-response data. Our initial intent with this study was to establish whether administering pregabalin at this selected high dose was effective in preventing chronic pain. Furthermore, large clinical studies with lower doses and shorter duration are necessary to determine the optimal dose and duration of intervention required to achieve similar results in this and other surgical pain models. Although the S-LANSS neuropathic pain ratings are a validated assessment tool,14 a full clinical examination of all patients enrolled in the study is always preferred. There was no difference in use of NSAIDs, opioids, or acetaminophen/tramadol between the pregabalin and placebo groups in the 6-mo postsurgery period. Placebo group patients were prescribed more gabapentin or pregabalin during this postoperative period than the pregabalin group. Interpretation of this for placebo patients is inconclusive without additional timeline and prescribing information, but does support the fact that the pregabalin group effect was the result of treatment dosing. Although ondansetron has been shown to produce modest transient analgesia in patients with neuropathic pain,40 the use of this drug was not increased in patients who did not develop neuropathic pain. Finally, because all of our patients had epidural analgesia, the results of this study may not apply to patients receiving perioperative IV or oral analgesics for TKA.

In summary, this study validates the efficacy of the perioperative use of pregabalin to reduce chronic neuropathic pain after TKA. In addition, pregabalin also shortens the time to achieve effective joint ROM.

REFERENCES


