A Prospective Randomized Trial on the Role of Perioperative Celecoxib Administration for Total Knee Arthroplasty: Improving Clinical Outcomes

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BACKGROUND: Total knee arthroplasty (TKA) is associated with considerable postoperative pain, which, if unrelieved, may result in prolonged hospital stay, inability to participate in rehabilitation programs, poor outcomes, and greater use of healthcare resources. The hypothesis of this study is that perioperative administration of celecoxib will improve analgesic efficacy, with a resultant improvement in short- and long-term clinical outcomes after TKA.

METHODS: We studied 200 patients undergoing elective TKA in a prospective, randomized, double-blind, placebo-controlled fashion. All patients underwent a similar perioperative anesthetic/analgesic procedure. After completion of surgery, patients were started on an epidural infusion with patient-controlled epidural analgesia. Patients were instructed to keep their numerical rating score pain ≤3. Patients were randomly assigned to one of two groups: celecoxib or placebo. The celecoxib group received celecoxib 100 mg orally twice a day 7 days before surgery. On the day of surgery, celecoxib 400 mg was administered 1–2 h before surgery and then 200 mg every 12 h for 10 postoperative days. The control group received matching placebo capsules at the same times. The primary objective of this study was to determine whether the perioperative use of celecoxib reduces the amount of postoperative opioid consumption. Secondary objectives were to determine whether celecoxib is associated with improved clinical outcomes and a reduction in opioid-related adverse effects.

RESULTS: The celecoxib group required less patient-controlled epidural analgesia over the 40-h postoperative period: placebo 232.8 ± 2.0 mL, celecoxib 209.1 ± 1.8 mL (P < 0.001). At home over days 4–10 after surgery, the celecoxib group had reduced pain intensity with movement (F = 109.7, P < 0.001) at all time points. The celecoxib group also consumed less oxycodone at home than placebo group (F = 417.8, P < 0.001). With active movement, range of motion (ROM) differed between the two groups over postoperative days 1–3 (F = 50.7, P < 0.001), with the celecoxib group having greater ROM at all time points. There was earlier achievement of 90 degrees knee flexion with celecoxib compared with placebo (P < 0.001). Celecoxib patients had a better overall Knee Society Score (93.3 ± 0.6) than placebo patients (86.4 ± 0.9) at 12-mo follow-up (P < 0.001). The incidence of side effects (nausea, vomiting, and pruritus) in the immediate postoperative period was less in the celecoxib group.

CONCLUSIONS: Perioperative use of celecoxib reduces postoperative pain, opioid consumption, opioid-related adverse effects, and is associated with long-term benefits including improved knee function and less time to achieve effective knee ROM after TKA.

(Total knee arthroplasty (TKA) has proven to be a successful surgical treatment of knee joints affected by osteoarthritis. Currently in the United States, more than 400,000 TKAs are performed every year with reported success rates ranging from 85% to 90%. In an aging population, the number of annual TKA procedures is expected to reach 3.48 million by the year 2030. TKA is associated with considerable postoperative pain, which, unrelied, may delay the patient’s eligibility for discharge, resulting in prolonged hospital stay, inability to participate in rehabilitation programs, delayed recovery, poor outcome, and greater use of healthcare resources. Patients unable to participate in a rehabilitation program after knee surgery.

Accepted for publication November 30, 2007.
Supported by an independent medical school grant from Pfizer, Inc., and from institutional and/or departmental sources.
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are at increased risk for developing postoperative knee complications, such as delay in strength recovery, prolonged stiffness, and may lead to chronic pain.6,7 Nonsteroidal antiinflammatory drugs (NSAIDs) are widely prescribed for patients with painful osteoarthritis, but because of the increased risk of perioperative bleeding, they are frequently discontinued 7–10 days before elective surgery.8 Continuing NSAIDs before total hip arthroplasty has been associated with a two-fold increase in the incidence of perioperative bleeding,9 although bleeding may be less of an issue with TKA due to use of tourniquet. A reduction in perioperative blood loss is a desirable goal, both from the point of view of facilitating the operative procedure, and reducing the risks of blood transfusion as well as wound hematoma, which could require further surgery. Discontinuing NSAIDs before surgery, however, can result in an arthritic flare, leading to increased preoperative pain. This may result in severe postoperative pain, since the intensity of preoperative pain has been shown to directly correlate with the severity of pain and amount of opioid analgesics required in the postoperative period after total joint arthroplasty.4,10 In addition, a flare-up of arthritis in other joints may interfere with postoperative physical therapy and rehabilitation. In a prospective, randomized, study of osteoarthritis patients undergoing TKA,11 the preoperative discontinuation of NSAIDs resulted in severe preoperative pain (Visual Analog Scale score >70 mm).

The use of cyclooxygenase-2 (COX-2) NSAIDs has been shown to offer a therapeutic advantage over standard NSAIDs for the management of perioperative pain for patients undergoing TKA.11–13 These studies have shown that the perioperative administration of COX-2 inhibitors does not result in an increased incidence of bleeding complications. Further, the perioperative use of COX-2 inhibitors for TKA was associated with reduced opioid consumption and improved outcome.12 The primary objective of this study was to determine whether the perioperative use of celecoxib reduces the amount of postoperative opioid consumption when analgesia is titrated to a numerical rating scale (NRS) score <4. Secondary objectives were to determine whether the use of celecoxib is associated with improved clinical outcomes and a reduction in opioid-related adverse effects in this setting.

**METHODS**

This was a prospective, randomized, double-blind, placebo-controlled study conducted March 2006 through February 2007. After IRB approval, written informed consent was obtained from 200 patients scheduled to undergo elective, unilateral TKA for osteoarthritis (Fig. 1). Patients were excluded if they were younger than 40 years or older than 80 years; ASA physical status IV; or with the diagnosis of rheumatoid arthritis, depression, or concurrent treatment with an antidepressant or anxiolytic, or concurrent musculoskeletal...
diagnosis that would affect the interpretation of pain (fibromyalgia, spinal stenosis). Additional exclusion criteria included an allergy to sulfa or celecoxib, creatinine level >1.5 mg/dL, or blood urea nitrogen level >22 mg/dL, or known coagulation disorder.

Study Design

All NSAIDs were discontinued 7 days before surgery. All patients underwent a similar perioperative anesthetic/analgesic protocol using a combined spinal-epidural technique with 10 μg intrathecal fentanyl. No intraoperative opioids or prophylactic antiemetics were used. After completion of the surgery, patients were started on an epidural infusion of fentanyl (5 μg/mL) and bupivacaine (1 mg/mL) as a continuous basal infusion (5 mL/h) superimposed with a patient-controlled epidural analgesia (PCEA) of 1 mL every 12 min with a 4-h lockout of 40 mL. Patients were instructed to keep their NRS pain <3 on a 0–10 scale with 0 representing no pain and 10 the worst imaginable pain. After 1 h, if the NRS score was >3 and the maximum number of PCEA boluses was used, morphine 1–2 mg IV was administered and the epidural basal infusion was increased by 1–2 mL/h. If the NRS score was <2, the basal epidural infusion was decreased by 1–2 mL/h. After 36 h postoperatively, patients were administered oxycodone 5–10 mg every 4 h as needed for a NRS score >3. In the absence of complications, by the morning of the third postoperative day, patients were discharged home or to a specific rehabilitation unit, depending on the level of independence and home support. All patients received home or outpatient physical therapy.

Patients were randomly assigned to one of two groups: celecoxib or placebo. Patients in the celecoxib group received celecoxib 100 mg orally twice per day 7 days before surgery. On the day of surgery, celecoxib 400 mg was administered 1–2 h before surgery and then 200 mg every 12 h for the first 10 postoperative days starting 12 h after surgery. The control group received matching placebo capsules at the same times pre- and postoperatively. For the 7 days before surgery, all patients were prescribed acetaminophen 500 mg/hydrocodone 5 mg, 1–2 tablets every 4–6 h as necessary for rescue analgesia. Acetaminophen/hydrocodone tablets were administered at least 1 h after study drug administration. Patients, nurses, and physicians were all blinded to treatment assignment.

Outcomes

Patients were asked to rate their average global pain intensity level for the first 7 days before surgery on a NRS from 0 to 10. In addition, patients were asked to record their preoperative use of acetaminophen/hydrocodone tablets. Postoperatively, NRS pain scores were recorded both at rest and with knee flexion every 8 h while in the hospital and then once daily at home. The total epidural medication consumption and number of delivered boluses were recorded for each 8-h interval postoperatively. On discharge from the hospital, patients were instructed to take oxycodone 5–10 mg every 4 h for a NRS score >3. Home NRS scores and oxycodone use were recorded by the patient in a diary and collected at the completion of the study.

Intraoperative blood loss was estimated by combining changes in sponge weights (assuming a density of 1 g/mL) with blood volume collected in the suction canister. Postoperative blood loss was determined from the drain output for the 24 h after surgery. The presence of postoperative nausea and vomiting (PONV) was individually categorized as a dichotomous (yes/no) variable every 8 h postoperatively while in the hospital. Patients with PONV were treated with IV ondansetron 4 mg and then IV metoclopramide 10 mg if needed.

The presence of postoperative pruritus was individually categorized as a dichotomous (yes/no) variable every 8 h postoperatively while in the hospital. Patients with pruritus were treated with IV nalbuphine 2 mg and then IV diphenhydramine 25 mg if needed. Sedation scores were measured on a NRS of 1–5 (1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep but not responsive to any stimulus) every 8 h postoperatively while in the hospital.

Physical therapy was initiated twice daily starting on the first postoperative day. Range of motion (ROM) of the knee was measured with a goniometer by a physical therapist. The degree of active and passive knee flexion tolerated by the patient and number of days required until obtaining 90 degrees of active knee flexion was recorded while in the hospital. In addition, ROM was assessed at 1 mo postoperatively.

Within 6 wk before surgery and at 12 mo postoperatively, a Knee Society Score (KSS)14 was completed, which has been widely accepted as an objective measure of knee status in patients undergoing TKA. The KSS clinical rating score ranges from 0 to 100 points (100 points being the best). The score allocates points for walking distance and stair-climbing ability and makes deductions for the use of a walking aid.

Patients rated their sleep disturbance during the previous 24 h each day while in the hospital on a 10-point scale (0 = no sleep disturbance to 10 = greatest sleep disturbance), which has been previously validated after TKA.12

Statistical Analysis

Sample size was estimated by analyzing previous data from studies comparing NRS pain scores between patients receiving another COX-2 inhibitor and those receiving placebo perioperatively for TKA.11 With 90% power, a medium effect size (0.5), and [α] = 0.05, a power analysis of t-test for two groups would...
require 85 patients per group. PCEA analgesic consumption, NRS pain scores at rest and with movement, home oxycodone use, active and passive ROM, sedation, and sleep were compared between the two groups over the postoperative time points with repeated measures linear fixed model. If group differences were significant ($P < 0.05$), then treatment groups were compared at each time point with Bonferroni-corrected post hoc $t$-test. Total PCEA analgesic use, NRS pain scores at 7 days before surgery, total acetaminophen/hydrocodone consumption over 7 days before surgery, intraoperative blood loss, supplementary IV morphine use, and ROM at 1 mo were compared between the two groups with $t$-test. Demographic data were analyzed using $t$-test or $\chi^2$ test, as appropriate. The incidence of each side effect was compared with $\chi^2$ test.

**RESULTS**

Of the 200 patients enrolled in the study (Fig. 1), 15 patients ($n = 6$ in placebo group and $n = 9$ in celecoxib group) dropped out because of protocol failure (unsuccessful spinal and/or epidural; required general anesthesia and/or femoral block). Another 11 patients enrolled but were either lost to follow-up or required surgery within 12 mo of follow-up ($n = 7$ placebo group, $n = 4$ celecoxib group). However, all of their data except for a 1-yr follow-up questionnaire were retained. Table 1 lists the characteristics of the 185 patients successfully completing the study. There were no differences in demographics, duration of surgery, or blood loss.

**Epidural Anesthetic Consumption**

Figure 2 shows the average PCEA-administered drug consumption at 8 h postoperative time intervals up to 40 h. Repeated measures analysis demonstrated a difference between the two groups ($F = 81.2, P < 0.001$) and also a group by time interaction ($F = 2.7, P = 0.030$). Post hoc analysis showed that the celecoxib group required less epidural solution at all time points. Total 40-h cumulative PCEA analgesic consumption was different between the two treatment groups ($P < 0.001$): placebo 232.8 $\pm$ 2.0 mL, celecoxib 209.1 $\pm$ 1.8 mL (mean $\pm$ SEM).

**Pain Scores and Supplemental Drug Consumption**

Over the 7 days before surgery, patients receiving celecoxib had lower overall pain scores at rest (3.42 $\pm$ 0.08 vs 5.28 $\pm$ 0.16, $P < 0.001$) and with movement (5.25 $\pm$ 0.10 vs 7.47 $\pm$ 0.16, $P < 0.001$) during that preoperative week and consumed less acetaminophen/hydrocodone analgesic (12.5 $\pm$ 0.4 g vs 34.9 $\pm$ 0.8 g, $P < 0.001$). The pain score was also lower on the morning of surgery for the celecoxib group (3.52 $\pm$ 0.07 vs 4.85 $\pm$ 0.14, $P < 0.001$). Over the initial 40-h PCEA infusion period, there were no differences in mean pain scores between the two groups of patients. NRS score at rest was 3.24 $\pm$ 0.04 in the placebo group and 3.25 $\pm$ 0.04 in the celecoxib group ($P = 0.89$); NRS score with movement was 5.39 $\pm$ 0.07 in the placebo group and 5.40 $\pm$ 0.07 in the celecoxib group ($P = 0.95$). Supplementary IV morphine use over this time period also showed no difference ($P = 0.954$): placebo 4.72 $\pm$ 0.37 mg, celecoxib 4.69 $\pm$ 0.38 mg (mean $\pm$ SEM).

Postoperative pain scores with movement over days 4 through 10 after surgery differed by group ($F = 109.7, P < 0.001$), and group by time ($F = 8.45, P < 0.001$). Post hoc testing showed that the celecoxib group had reduced pain intensity at all time points (Fig. 3). At rest, pain scores also differed between the two groups ($F = 69.5, P < 0.001$), and also group by time ($F = 5.91, P < 0.001$). Post hoc analysis showed that the celecoxib group had reduced pain intensity at all time points, except on day 5. Home oxycodone use also differed between the two groups ($F = 417.8, P < 0.001$), and also group by time ($F = 10.4, P < 0.001$). Post hoc testing showed that the celecoxib group consumed less oxycodone than the placebo group at all time points.

**ROM**

Figure 4 displays the active ROM as evaluated in the hospital over the initial three postoperative days. ROM differed between the two groups ($F = 50.7, P < 0.001$), and also group by time ($F = 8.58, P < 0.001$). Post hoc analysis showed that the celecoxib group had greater ROM at all time points. With passive knee

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**Table 1. Patient Demographics and Surgical Data**

<table>
<thead>
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<th>Treatment group</th>
<th>Placebo</th>
<th>Celecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
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</tr>
<tr>
<td>Gender (M/F)</td>
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<td>46/45</td>
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<tr>
<td>Age (yr)</td>
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<td>Weight (kg)</td>
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<td>Height (cm)</td>
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<tr>
<td>Duration of surgery (min)</td>
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<td>95 $\pm$ 7</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>289 $\pm$ 15</td>
<td>286 $\pm$ 16</td>
</tr>
</tbody>
</table>

Data are presented as mean $\pm$ sd.
movement, ROM differed between the two groups ($F = 68.6$, $P < 0.001$), but not group by time ($F = 1.71$, $P = 0.129$). Post hoc analysis again showed that the celecoxib group had greater ROM at all time points. At the time of ROM evaluation, NRS pain scores were also obtained. The NRS score at the time of active testing differed between the two groups ($F = 27.1$, $P < 0.001$), but not group by time ($F = 1.38$, $P = 0.253$). Post hoc analysis showed that on each day, the celecoxib group had reduced pain scores (e.g., day 3, 3.25 ± 0.09 vs 3.81 ± 0.10, $P = 0.0012$). Similarly, the NRS score at the time of passive testing differed between the two groups ($F = 124.1$, $P < 0.001$), but not group by time ($F = 0.93$, $P = 0.396$). Post hoc analysis showed that the celecoxib group had reduced pain scores on each day.

Although short-term ROM outcomes are important for discharge home and to achieve simple daily activities, long-term ROM outcomes are of greater significance. Figure 5 displays the number of days needed to achieve the milestone of 90 degrees active flexion.

Kaplan–Meier analysis demonstrated earlier achievement of 90 degrees knee flexion with celecoxib compared with placebo ($P < 0.001$). Active flexion at 1 mo after TKA was greater in the celecoxib group than in the placebo group (105.7 ± 0.7 vs 99.4 ± 0.7, $P < 0.001$). There was no difference in the KSS before surgery, but celecoxib patients had a higher (better) overall score (93.3 ± 0.6) than placebo patients (86.4 ± 0.9) at 12-mo follow-up ($P < 0.001$).

**Side Effects**

Table 2 summarizes the incidence of side effects in the immediate postoperative period. Fewer patients experienced nausea in the celecoxib group (8.8%) compared with the placebo group (30.9%). Vomiting was less frequent in the celecoxib group (6.6%) than in the placebo group (21.2%). Use of antiemetics was also reduced in the celecoxib group. Fewer patients received ondansetron in the celecoxib group (8.8%) than in the placebo group (27.6%); fewer patients received metoclopramide in the celecoxib group (3.3%) than in the placebo group (14.9%). The incidence of pruritus was less in the celecoxib group (16.5%) than with placebo (30.9%). Fewer patients received nalbuphine in the celecoxib group (17.6%) than in the placebo group (33.0%); fewer patients received diphenhydramine in the celecoxib group (4.4%) than in the placebo group (13.8%). Mean sedation scores (1–5 scale) over the 40-h postoperative period were slightly better in

**Table 2. Incidence of Side Effects**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Placebo</th>
<th>Celecoxib</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
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<td>Number</td>
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<td>91</td>
<td>&lt;0.001</td>
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<td>Nausea</td>
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<td>8</td>
<td>0.004</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>6</td>
<td>0.001</td>
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<td>Ondansetron given</td>
<td>26</td>
<td>8</td>
<td>0.006</td>
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<tr>
<td>Metoclopramide given</td>
<td>14</td>
<td>3</td>
<td>0.022</td>
</tr>
<tr>
<td>Pruritus</td>
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<td>0.016</td>
</tr>
<tr>
<td>Nalbuphine given</td>
<td>31</td>
<td>16</td>
<td>0.026</td>
</tr>
<tr>
<td>Diphenhydramine given</td>
<td>13</td>
<td>4</td>
<td>0.026</td>
</tr>
</tbody>
</table>

**Figure 3.** Numerical rating scale (NRS) pain with movement evaluated at home over postoperative days 4–10. The group receiving celecoxib experienced less pain. Data are shown as mean ± sem; *different from placebo ($P < 0.01$).

**Figure 4.** Active range of motion evaluated on postoperative days 1–3. The group receiving celecoxib had greater range of motion. Data are shown as mean ± sem; *different from placebo ($P < 0.001$).

**Figure 5.** Kaplan–Meier analysis of time to achieve 90 degrees active knee flexion after total knee arthroplasty. The celecoxib group reached 90 degrees earlier (log rank $P < 0.001$).
Although pain scores are typically the primary outcome measured in clinical pain studies, this trial was designed for greater clinical relevancy by having patients titrate PCEA to achieve comfort. Such use of PCEA facilitated demonstration of reduced patient-determined requirement for analgesia in the celecoxib group (Fig. 2), similar to a previous trial. There was also reduced consumption of oxycodone at home from days 4–10 after surgery in the celecoxib group compared with placebo, as well as decreased NRS pain scores with movement (Fig. 3) or at rest.

The reduced narcotic consumption in the celecoxib group also led to decreased incidence of nausea (8.8% vs 30.9%) and vomiting (6.6% vs 21.2%) and antiemetic therapy. Several factors are associated with PONV after regional anesthesia. Although reduced opioid consumption and improved analgesia may have been responsible for reduced PONV in our study, COX-2 inhibition alone can prevent pharmacologically induced emesis in animals.

The purpose of the 7-day preoperative dosing of celecoxib was not intended to be used as a preemptive analgesic, but rather to avoid an arthritic flare due to discontinuing NSAIDs before surgery. Indeed, the presurgical NRS score was lower in the celecoxib group than in the placebo. It is possible that the lower PCEA consumption and even the decreased active and passive NRS pain scores during ROM testing on postoperative days 1–3 were due primarily to the reduced preoperative pain in that group. In addition to improving short-term outcomes, it is possible that controlling pain in the preoperative period may contribute to improved long-term outcomes. It has been demonstrated that heightened preoperative pain (NRS score >4) before TKA is an independent risk factor for increased postoperative pain and opioid use, longer hospital length of stay, longer inpatient rehabilitation stay, more home physical therapy visits, lower knee ROM, and worse knee function scores 1 yr after surgery. We believe that the improved outcomes demonstrated in the present study were due to the effective pain control throughout the entire perioperative period, thus allowing these patients to actively participate in a rehabilitation program. We have previously demonstrated that the sustained administration of celecoxib as a component of a multimodal analgesic technique contributes to a significant reduction in both acute postoperative pain and long-term patellofemoral complications, and improvement in knee function scores after major knee surgery.

The current data reinforce the concept that pain management is important during all aspects of the surgical continuum, from the perioperative to postdischarge and recovery periods.

One might conceive of an alternative study protocol by which the control group received short-acting NSAIDs (rather than placebo), over the same 7-day preoperative period that would be interrupted a day...
before surgery to avoid perioperative bleeding.29 However, routine practice in the United States is still to discontinue all NSAIDs for 7 days before major surgery, and since there is no published clinical trial demonstrating that there is no increased risk of bleeding with a NSAID maintained up to 24 h before surgery, we were limited in our study to using preoperative placebo in our control group.

In summary, this study validates the efficacy of perioperative use of celecoxib to reduce postoperative pain and opioid consumption after major orthopedic surgery. Moreover, our findings indicate that preoperative COX-2 inhibition along with continuation of COX-2 inhibition during the postoperative and rehabilitative phases has important long-term outcome benefits after TKA, including less time to achieve effective joint ROM and improved knee function at 1 yr after surgery.

REFERENCES