Effects of Perioperative Administration of a Selective Cyclooxygenase 2 Inhibitor on Pain Management and Recovery of Function After Knee Replacement: A Randomized Controlled Trial

Asokumar Buvanendran, MD
Jeffrey S. Kroin, PhD
Kenneth J. Tuman, MD
Timothy R. Lubenow, MD
Dalia Elmofty, MD
Mario Moric, MS
Aaron G. Rosenberg, MD

POSTOPERATIVE PAIN AFFECTS A variety of physiological functions and can adversely influence surgical outcome. Efficient management of acute postoperative pain has been demonstrated to improve clinical outcomes and effective postoperative analgesia is part of a major initiative for US hospitals, with the introduction of pain as the fifth monitored vital sign.

Surgical trauma induces cyclooxygenase 2 (COX-2) and subsequent synthesis of prostaglandins that sensitize peripheral nociceptors and mediate central sensitization. In addition to analgesic synergism with opioids, nonsteroidal anti-inflammatory drugs (NSAIDs) decrease this inflammatory response associated with surgery. There is evidence that prostaglandin synthesis plays a role in postoperative orthopedic pain. Inadequate control of postoperative pain has been associated with poor functional recovery after total knee arthroplasty (TKA). Preoperative administration of NSAIDs may be effective by establishing a sufficient tissue NSAID concentration to prove clinical outcome and effective pain has been demonstrated to improve management of acute postoperative administration of NSAIDs may be effective by establishing a sufficient tissue NSAID concentration to reduce inflammatory responses.

Pulmonary complications associated with surgery are a major concern in orthopedic surgery. The use of selective COX-2 inhibitors has been shown to reduce the risk of gastrointestinal complications associated with nonselective NSAIDs. However, the impact of these agents on postoperative pain and functional outcomes after total knee arthroplasty is not well understood.

Objective To assess the effect of combined preoperative and postoperative administration of a selective inhibitor of cyclooxygenase 2 on opioid consumption and outcomes after total knee arthroplasty (TKA).

Design, Setting, and Patients Randomized, placebo-controlled, double-blind trial conducted June 2001 through September 2002, enrolling 70 patients aged 40 to 77 years and undergoing TKA at a university hospital in the United States.

Interventions Patients were randomly assigned to receive 50 mg of oral rofecoxib at 24 hours and at 1 to 2 hours before TKA, 50 mg daily for 5 days postoperatively, and 25 mg daily for another 8 days, or matching placebo at the same times.

Main Outcome Measures Postoperative outcomes including postsurgical analgesic consumption and pain scores achieved, nausea and vomiting, joint range of motion, sleep disturbance, patient satisfaction with analgesia, and hematologic and coagulation parameters.

Results Total epidural analgesic consumption and in-hospital opioid consumption were less in the group receiving rofecoxib compared with the group receiving placebo (P < .05). Median pain score (visual analog scale [VAS], 0-10) achieved for the knee was lower in the rofecoxib group compared with the placebo group during hospital stay (2.2 [interquartile range (IQR), 1.4-3.2] vs 3.5 [IQR, 2.7-4.3], P < .001) and 1 week after discharge (2.6 [IQR, 1.4-3.5] vs 3.7 [IQR, 2.9-4.7], P = .03). There was less postoperative vomiting in the rofecoxib group (6%) compared with the placebo group (26%) (P = .047), as well as a decrease in sleep disturbance compared with the placebo group on the night of surgery (P = .006) and on the first (P = .047) and second (P < .001) days postoperatively. Knee flexion was increased in the rofecoxib group compared with the placebo group at discharge (active flexion: mean [SD], 84.2° [11.1°] vs 73.2° [13.6°], P = .03; passive flexion: 90.5° [6.8°] vs 81.8° [13.4°], P = .05) and at 1 month postoperatively (109.3° [8.5°] vs 100.8° [11.8°], P = .01), with shorter time in physical therapy to achieve effective joint range of motion. The rofecoxib group was more satisfied with analgesia and anesthetica at discharge compared with the placebo group (median satisfaction score, 4.3 [IQR, 3.0-4.7] vs 3.3 [IQR, 2.3-4.3], respectively; P = .03), and the differences persisted at 2-week and at 1-month follow-up. There was no intergroup difference in surgical blood loss (P > .05 for both intraoperative and postoperative blood loss).

Conclusion Perioperative use of an inhibitor of cyclooxygenase 2 is an effective component of multimodal analgesia that reduces opioid consumption, pain, vomiting, and sleep disturbance, with improved knee range of motion after TKA.

©2003 American Medical Association. All rights reserved.

(Reprinted with Corrections) JAMA, November 12, 2003—Vol 290, No. 18 2411

Author Affiliations are listed at the end of this article.
Corresponding Author and Reprints: Asokumar Buvanendran, MD, Department of Anesthesiology, 1653 W Congress Pkwy, Rush-Presbyterian-St Luke’s Medical Center, Chicago, IL 60612 (e-mail: Asokumar @aol.com).

www.jama.com
inhibit the early production of prostanooids before the onset of tissue trauma, thus attenuating the development of hyperalgesia. However, nonselective use of NSAIDs is often limited in surgical patients because of concerns about increased bleeding. NSAIDs are frequently discontinued 7 to 10 days before elective orthopedic surgery because studies have demonstrated that continuing nonselective NSAID therapy is associated with a 2-fold increase in blood loss after hip arthroplasty.

Selective COX-2 inhibitors have little or no effect on coagulation and are therefore attractive for use in the surgical setting. Rofecoxib, an oral selective COX-2 inhibitor, has been approved for the treatment of acute postoperative pain. Although preoperative administration of rofecoxib can reduce pain after knee arthroscopic surgery as well as decrease opioid requirements after spinal fusion surgery and otolaryngologic procedures, other outcome benefits have not been demonstrated. A single preoperative dose of rofecoxib, however, has not been shown to be effective in reducing pain after radical prostatectomy. Indeed, analgesic therapy initiated preemptively and continued postoperatively may reduce both incisional and inflammatory pain as well as peripheral and central neural sensitization, and may improve outcome. This study was designed to test the hypothesis that preoperative administration of a COX-2 inhibitor, followed by continued postoperative administration, reduces opioid requirements and improves clinical outcomes after TKA.

**METHODS**

**Participants**

The study was a randomized, placebo-controlled, double-blind trial conducted June 2001 through September 2002, enrolling patients undergoing TKA. After approval of the Rush-Presbyterian-St Luke’s Medical Center institutional review board, consecutive patients scheduled to undergo elective primary TKA were contacted and assessed for study eligibility with a screening medical history (FIGURE 1). All prior NSAID therapy was discontinued 14 days prior to surgery. After providing written informed consent, each patient was allocated a study number; a dispensing pharmacist had knowledge of the study codes. Treatment assignment codes were not available to the investigators until all patients completed the study.

Sample sizes were chosen to detect clinically relevant differences using a power analysis based on previously published data evaluating the effect of rofecoxib on opioid consumption after spinal fusion surgery. A sample size of 35 patients per group was chosen to provide greater than 90% power to detect differences.

**Interventions**

Patients in the rofecoxib group received 50 mg of rofecoxib orally, 24 hours before and 1 to 2 hours before the surgery. Patients randomized to this group also received 50 mg of rofecoxib orally once daily on postoperative days 1 through 5. Beginning on the sixth postoperative day they received 25 mg of rofecoxib orally once daily for another 8 days. The control group received placebo doses at the same times preoperatively and postoperatively.

The study patients were blinded to group assignments, as were the physicians and nurses managing the patient during surgery and in the recovery room, and as were the personnel involved with postoperative pain assessment and management of the epidural infusion. During the conduct of the study, only the dispensing pharmacist had knowledge of the study codes. Treatment assignment codes were not available to the investigators until all patients completed the study.

Sample sizes were chosen to detect clinically relevant differences using a power analysis based on previously published data evaluating the effect of rofecoxib on opioid consumption after spinal fusion surgery. A sample size of 35 patients per group was chosen to provide greater than 90% power to detect differences.

### Figure 1. Flow of Patients Through the Trial

254 Patients Assessed for Eligibility

- 184 Not Enrolled
- 70 Randomized

- 35 Assigned to Receive Placebo
  - 2 Withdrawn
    - 1 Unable to Insert Epidural Catheter
    - 1 Epidural Infusion Stopped for Assessment of Postoperative Foot Drop
  - 33 Completed Protocol
  - 34 Included in Modified Intent-to-Treat Analysis
    - 1 Excluded (Unable to Insert Epidural Catheter)

- 35 Assigned to Receive Rofecoxib
  - 2 Withdrawn
    - 1 Unable to Obtain CSF When Initiating Combined Spinal-Epidural Anesthesia
    - 1 Epidural Catheter Removed Prior to Heparinization for Pulmonary Embolus
  - 33 Completed Protocol
  - 34 Included in Modified Intent-to-Treat Analysis
    - 1 Excluded (Unable to Obtain CSF)

CSF indicates cerebrospinal fluid.
Algesia was assessed 1 hour after commencement of the epidural infusion using the VAS. If the VAS score was 4 or greater and the maximum number of PCEA boluses was used, patients received 1 to 2 mg of intravenous morphine (maximum, 10 mg over 2 hours). If the VAS score remained 4 or greater after 4 hours of the epidural infusion, the epidural catheter was tested for proper position with 3 mL of lidocaine (20 mg/mL) containing epinephrine. If the test dose produced sensory analgesia the epidural infusion was increased in increments of 1 to 2 mL/h to achieve a VAS score less than 4. If the VAS score was 2 or less after 4 hours without any PCEA doses, the basal epidural infusion was decreased by 1 to 2 mL/h and the patient was reminded to use PCEA to maintain the desired level of analgesia. When the epidural infusion was discontinued (between 36-42 hours) patients were transitioned to oral hydrocodone (5 mg every 4-6 hours as needed), unless allergy necessitated use of propoxyphene.

**Objectives**

The primary objective was to determine whether perioperative use of a selective COX-2 inhibitor reduced the amount of postoperative opioid consumption when analgesia was titrated to a standard goal (VAS score of 2-4) after TKA. The secondary objective was to determine if perioperative use of rofecoxib was associated with improved clinical outcome (and/or decreased adverse effects) in this setting.

**Outcome Measures**

**Epidural and Pain Assessment.** Pain scores using the VAS for the operated knee were assessed in the recovery room, 1 hour after epidural infusion was commenced, and every 8 hours for the immediate postoperative phase (24 hours). The total (continuous and PCEA mode) epidural medication consumption, total number of PCEA demands, and number of delivered boluses were recorded for each 4-hour interval postoperatively. All other opioid consumption was recorded and subsequently converted to parenteral morphine-equivalents (5 mg of hydrocodone was considered to be equivalent to 2.5 mg of parenteral morphine) for statistical comparisons. The VAS score was assessed twice daily for the duration of the hospital stay (3-4 days) and then once daily at home for 2 weeks. Home VAS scores were recorded by the patient in a diary and collected at completion of the study.

**Sleep and Satisfaction.** Patients rated sleep disturbance during the previous 24 hours for each day of the hospital stay (10-point scale: 0 = no sleep disturbance, 10 = greatest sleep disturbance). Patient satisfaction with regard to hospitalization, course of treatment, anesthesia, and analgesia (assessed using 5-point scale: 1 = no efficacy and 5 = excellent efficacy) was de-

**Protocol**

Demographic data were recorded during the preoperative visit. A pain score for the operated knee was assessed using a visual analog scale (VAS) with 0 corresponding to “no pain” and 10 to “the worst imaginable pain.” In the operating room, patients were sedated with midazolam (0.05 mg/kg, titrated to effect) and a combined spinal-epidural procedure performed in the sitting position, at the L2-3 or L3-4 vertebral level. If clear cerebrospinal fluid (CSF) was not obtained the patient was removed from the study. After obtaining clear CSF, 1.5 mL of 0.75% hyperbaric bupivacaine with 25 µg of fentanyl was injected. After the intrathecal injection, an epidural catheter was inserted 3 to 5 cm into the epidural space. Prior to administering spinal anesthetic, 0.5 mL of CSF was removed and venous blood (5 mL) was simultaneously sampled from odd-numbered study patients for the analysis of CSF and plasma rofecoxib concentrations. A sensory analgesic level of T10 was obtained prior to commencement of surgery. Patients were sedated with intravenous propofol (50-75 µg/kg per hour) for the duration of surgery. Heart rate, blood pressure, oxygen saturation, temperature, and respiration were monitored per American Society of Anesthesiologists guidelines. A standardized surgical technique was used in all patients, including a thigh tourniquet inflated to 300 to 350 mm Hg after exanguination of the limb with an Esmarch bandage.

At completion of surgery an epidural infusion of fentanyl (10 µg/mL) and bupivacaine (1 mg/mL) was initiated using a continuous basal infusion with superimposed patient-controlled epidural analgesia (PCEA) bolus doses. Patients initially received a 5-mL/h basal epidural infusion, plus PCEA of 1 mL every 12 minutes with a 4-hour lockout of 40 mL. The patients were instructed prior to surgery to use the PCEA mode at their discretion to maintain the VAS pain score between 2 and 4.

©2003 American Medical Association. All rights reserved.

(Reprinted with Corrections) JAMA, November 12, 2003—Vol 290, No. 18  2413

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 09/29/2019
Race, No. (%)

<table>
<thead>
<tr>
<th>Race</th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>33 (94)</td>
<td>29 (83)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6)</td>
<td>6 (17)</td>
</tr>
</tbody>
</table>

Sex, No. (%)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>20 (57)</td>
<td>27 (77)</td>
</tr>
<tr>
<td>Men</td>
<td>15 (43)</td>
<td>8 (23)</td>
</tr>
</tbody>
</table>

Duration of tourniquet application, mean (SD), min

<table>
<thead>
<tr>
<th>Duration</th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.3 (18.8)</td>
<td>88.1 (24.3)</td>
<td></td>
</tr>
</tbody>
</table>

Intraoperative fluid therapy, mean (SD), L

<table>
<thead>
<tr>
<th>Intraoperative fluid therapy</th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 (0.5)</td>
<td>2.1 (0.6)</td>
<td></td>
</tr>
</tbody>
</table>

Duration of anesthesia, mean (SD), min

<table>
<thead>
<tr>
<th>Duration</th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>143.1 (23.5)</td>
<td>148.0 (24.9)</td>
<td></td>
</tr>
</tbody>
</table>

PGI2 has been shown to increase peripherally and locally. 

Plasma and CSF Analysis of Rofecoxib. The CSF and venous blood samples drawn at the initiation of combined spinal-epidural anesthesia were frozen at −80°C. All samples were sent frozen to Merck Frosst Canada (Kirkland, Quebec) for assay of rofecoxib concentration using high-pressure liquid chromatography, as previously described.23 The detection level for free rofecoxib was 0.02 µg/mL in CSF and 0.05 µg/mL in plasma.

Hematologic Evaluation. A complete blood cell count, platelet count, prothrombin time (PT), and international normalized ratio (INR) were obtained preoperatively. Intraoperative blood loss was estimated from surgical sponges and from blood volume measured in a suction canister prior to wound irrigation. Postoperative blood loss was assessed by measuring the amount of blood collected in a knee drainage device (ConstaVac CBCII Blood Conservation System, Stryker Corp, Kalamazoo, Mich) during the first 24 hours. Any blood product transfused in the perioperative phase was recorded. Postoperatively, complete blood cell count, PT, and INR were obtained daily and the doses of warfarin prescribed by a hematologist (blinded to study group) to achieve the therapeutic effect for thromboembolism prophylaxis were recorded.

Statistical Methods

Demographic data were analyzed using t tests, χ² tests, and Fisher exact tests, as appropriate. Correspondingly, descriptive statistics are reported as mean and SD for continuous normally distributed variables, or as median and interquartile range (IQR) for ordinal or nonnormally distributed variables. Dichotomous variables are reported using counts and/or percentages.

Variables with measures at multiple time points were analyzed using repeated-measures analysis of variance to account for the correlated nature of individual patient contributions. The primary and secondary study hypotheses determined the form and construction of the preplanned comparisons, which were evaluated using a bootstrap method to control for multiple comparisons.24 End points of interest were analyzed using analysis of variance, t tests, the Mantel-Haenszel test, or the Mann-Whitney U test, contingent on the scale and distributional characteristics of the variables, and applying the Bonferroni correction method to adjust for multiple comparisons. Relationships between variables were evaluated using either the Pearson product-moment correlation or the Spearman rank-order correlation (for ordinal data), with modeling performed using simple linear regression. The log-rank statistic was used to test differences between groups in the Kaplan-Meier analyses for achievement of 90° knee flexion. All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC; P<.05 was used to determine statistical significance).

RESULTS

Study Population

The characteristics of the 70 patients who were included in the intent-to-treat analysis are shown in Table 1. There were no differences in demographic characteristics, surgical duration, intraoperative hemodynamic pa-
rameters, or amount of fluid therapy between study groups.

A total of 70 patients were enrolled in the study, with 66 (94%) completing the study (Figure 1). The percentage of patients who completed the study did not differ between treatment groups. One patient in the rofecoxib group had early study termination due to pulmonary embolus and 1 patient in the placebo group had the epidural infusion stopped to evaluate new-onset foot drop. There was technical failure to initiate combined spinal-epidural anesthesia in 2 patients, who were immediately withdrawn from the study. Because a primary outcome variable was opioid consumption, the modified intent-to-treat analysis was applied to 68 patients. Statistical outcomes did not change when the sample was restricted to the intent-to-treat population compared with the cohort completing the protocol (n=66).

Outcomes

Figure 2 shows the average epidural drug consumption at each of the postoperative time intervals. The total epidural drug consumption measured over 42 hours postoperatively was less in the rofecoxib group compared with the placebo group (mean [SD], 252.0 [65.5] mL vs 302.6 [62.7] mL, respectively; P<.001), and a similar decrease in pain score was observed 1 week after discharge from the hospital (median [IQR] pain score, 2.6 [1.4-3.5] vs 3.7 [2.9-4.7], respectively; P=.03) (Table 2). The mean length of stay was 3.2 (IQR, 3-4) days for the rofecoxib group vs 3.3 (IQR, 3-4) days for the placebo group.

PCEA to achieve a VAS score of 4 or less for pain in the operated knee during the immediate postoperative period, the mean VAS score for the knee was less in the rofecoxib group compared with the placebo group during the hospital stay (FIGURE 3). Median VAS scores showed a similar relationship for the same time period (median [IQR] pain score, 2.2 [1.4-3.2] vs 3.5 [2.7-4.3]) for the rofecoxib group versus the placebo group, respectively (P<.001), and a similar decrease in pain score was observed 1 week after discharge from the hospital (median [IQR] pain score, 2.6 [1.4-3.5] vs 3.7 [2.9-4.7], respectively; P=.03) (Table 2). The mean length of stay was 3.2 (IQR, 3-4) days for the rofecoxib group vs 3.3 (IQR, 3-4) days for the placebo group.

Nausea and Vomiting. There was a decrease in the incidence of postoperative vomiting in the rofecoxib group compared with the placebo group on the first postoperative day (Table 3). In the rofecoxib group, there was also a lower incidence of nausea (24%, compared with 44% in the placebo group; P=.08) but this did not achieve statistical significance. Fewer patients received antiemetic therapy for PONV in the rofecoxib group compared with the placebo group.

Sleep Disturbance. There was a decrease in sleep disturbance on the first

---

**Table 2. Postoperative Analgesic Consumption and Pain Scores**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rofecoxib</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCEA doses, median (IQR), No. Requested</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 h</td>
<td>27.5 (15.0-37.5)</td>
<td>11.0 (6.0-26.0)</td>
<td>.15</td>
</tr>
<tr>
<td>12-24 h</td>
<td>16.5 (7.5-29.0)</td>
<td>8.0 (3.0-13.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Total</td>
<td>41.0 (23.0-72.0)</td>
<td>21.0 (13.0-39.0)</td>
<td>.04</td>
</tr>
<tr>
<td>Delivered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 h</td>
<td>13.5 (9.5-17.0)</td>
<td>8.0 (5.0-13.0)</td>
<td>.04</td>
</tr>
<tr>
<td>12-24 h</td>
<td>10.0 (6.0-14.5)</td>
<td>6.0 (2.0-11.0)</td>
<td>.045</td>
</tr>
<tr>
<td>Total</td>
<td>23.5 (15.0-30.5)</td>
<td>16.0 (9.0-21.0)</td>
<td>.02</td>
</tr>
</tbody>
</table>

---

**Figure 3. Postoperative Pain Score During Hospitalization After Total Knee Arthroplasty**

VAS indicates visual analog scale (0-10). Error bars indicate SD.
3 nights following surgery for the patients randomized to receive rofecoxib vs placebo (first night: median [IQR], 0.5 [0-4.5] points vs 5.0 [1.5-8.5] points, respectively; *P*=.006; second night: 0 [0-1] points vs 1 [0-5] points, *P*=.047; third night: 0 [0-0] points vs 4 [2-5] points, *P*<.001). Sleep disturbance on the night of surgery was positively correlated with PCEA demand (*P*=.02; *r*=0.4) and negatively correlated with the plasma level of rofecoxib obtained at the time of surgery (*P*=.03; *r*=-0.6).

**Plasma and CSF Rofecoxib Level.** Eighteen patients in the rofecoxib group had plasma and CSF samples drawn for rofecoxib analysis. The mean plasma concentration of rofecoxib was 0.503 (SD, 0.198) µg/mL and the mean CSF concentration of rofecoxib was 0.033 (SD, 0.013) µg/mL. The CSF/plasma ratio of rofecoxib was 0.073 (SD, 0.030). The CSF concentration of rofecoxib increased (*P*=.002) and the 4-hour postoperative epidural drug consumption decreased (*P* =.02) as plasma level of rofecoxib increased. The patients who had plasma and CSF sampled for assays were not demographically different from the remaining patients in the rofecoxib group. There were no detectable levels of rofecoxib in any of the assayed placebo patients (n=17).

**Hematologic Data.** There were no differences in the preoperative complete blood cell count, PT, or INR between the 2 groups. There was no change in the hemoglobin concentration between the 2 groups in the postoperative period. Three patients received 1 unit of autologous blood transfusion: 2 in the placebo group and 1 in the rofecoxib group. There was no difference in the intraoperative or postoperative mean (SD) blood loss between study groups (intraoperative: 111.8 [110.0] mL vs 80.5 [56.9] mL for rofecoxib vs placebo, respectively, *P* =.30; postoperative: 364.1 [231.3] mL vs 395.6 [286.3] mL, *P*>.99). There was no difference in the amount of warfarin prescribed between the 2 groups (mean [SD] total prescribed over 4 days: 13.32 [3.95] mg vs 12.44 [3.37] mg for rofecoxib vs placebo, respectively, *P*=.42), and the INR and PT were similar for the 2 groups (data not shown; *P*>.05 for all comparisons).

**Satisfaction With Anesthesia and Analgesia.** The rofecoxib group had higher satisfaction with anesthesia and analgesia at discharge (median [IQR] satisfaction score, 4.3 [3.0-4.7]) compared with the placebo group (3.3 [2.3-4.3]) (*P*=.03). The difference in satisfaction measured at discharge from the hospital persisted at both 2-week (*P*=.03) and 1-month (*P*=.03) follow-up. At 2 weeks and 1 month postoperatively, patients in the placebo group who had PONV while in the hospital were most dissatisfied.

**Adverse Events**

None of the patients had any bleeding complications requiring therapy. One patient in the rofecoxib group had the epidural catheter removed prior to heparinization for documented pulmonary embolus. One patient in the placebo group developed a foot drop on the operated side after surgery and epidural analgesia was discontinued while assessing etiology.

### Table 3. Postoperative Nausea and Vomiting, Use of Antiemetic Medications, and Range of Motion of the Operated Knee

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (44)</td>
<td>8 (24)</td>
<td>.08</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (26)</td>
<td>2 (6)</td>
<td>.047</td>
</tr>
<tr>
<td>Antiemetic use</td>
<td>14 (41)</td>
<td>6 (18)</td>
<td>.04</td>
</tr>
</tbody>
</table>

**Range of Motion, Mean (SD), Degrees**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 35)</th>
<th>Rofecoxib (n = 35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active flexion</td>
<td>73.2 (13.6)</td>
<td>84.2 (11.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Passive flexion</td>
<td>81.8 (13.4)</td>
<td>90.5 (6.8)</td>
<td>.05</td>
</tr>
<tr>
<td>1 Month postoperative*</td>
<td>100.8 (11.8)</td>
<td>109.3 (8.5)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Based on active flexion only.

**Figure 4. Kaplan-Meier Analysis of Time to Achieve 90° Knee Flexion After Total Knee Arthroplasty**

The main findings of this randomized study are that preoperative administration of the COX-2 inhibitor rofecoxib, followed by continued postoperative administration, reduces opioid requirements and improves measured clinical outcomes after TKA. Failure to demonstrate a beneficial outcome effect of preemptive analgesia in several clinical trials may be attributable either to insufficient peri-
operative nociceptive afferent blockade or to the development of central sensitization once the pharmacological action of the initial preemptive analgesic has dissipated. Outcome benefits may accrue from extension of specific preemptive analgesic therapy initiated preoperatively into the postoperative period. Continuation of preoperative COX-2 inhibitor therapy during the postoperative and rehabilitative phase with maintained blockade of the inflammatory and prostanoid-mediated responses associated with orthopedic surgery was therefore hypothesized to improve postoperative outcome. A long-acting COX-2 inhibitor such as rofecoxib (effective half-life, 17.5 hours) that can be ingested without food by a fasting preoperative patient was chosen for study because these characteristics are favorable to such perioperative use.

Although pain scores are typically the primary outcome measured in clinical pain studies, this trial was designed for greater clinical relevance by having patients titrate PCEA to achieve a reasonable level of comfort (defined as a VAS score of 2-4). Such use of PCEA facilitated demonstration of reduced patient-determined requirement for epidural local anesthetic and opioid in the rofecoxib group. Patients in the rofecoxib group also consumed less parenteral and oral opioid while having lower mean pain scores during and after hospitalization. In addition to these analgesic benefits, patients receiving rofecoxib had less PONV and antiemetic therapy. Several factors are associated with PONV after regional anesthesia, including use of opioids and amount of postoperative pain. While reduced opioid consumption and improved analgesia may be responsible for reduced PONV in this study, COX-2 inhibition alone can prevent pharmacologically induced emesis in animals. Consistent with other data, the reduction of PONV in the rofecoxib group was the predominant determinant of patient satisfaction, although other factors such as quality of analgesia and improved recovery of knee function (ie, range of motion) may have influenced satisfaction scores.

Range of motion is an important measure of outcome after TKA. It has been demonstrated that, after TKA, 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. Further improvement in the range of motion to 106° is required for activities such as tying shoelaces. The active knee flexion (73.2°) attained in our placebo group is similar to that reported in other studies using postoperative regional analgesia after TKA, while the rofecoxib group demonstrated greater knee functionality (84.2° active flexion) at discharge. It is likely that this beneficial effect on knee function at discharge facilitated attainment of nearly full functionality (range of motion, >106°) in the rofecoxib group at 1 month after surgery. These beneficial effects have important economic implications for reducing the significant costs associated with the additional time and physical therapy needed to achieve full knee function observed when patients did not receive rofecoxib.

Total sleep time and rapid eye movement sleep are typically reduced after surgery and anesthesia. Although the decreased sleep disturbance observed in the rofecoxib group appears to correlate with plasma concentration of rofecoxib, our study design does not permit identification of specific mechanisms for this association. It is plausible that reduced use of opioids may be a factor, since opioids are known to disturb normal sleep patterns despite inducing sedation. The increased need to use the PCEA mode also may have contributed to greater sleep disturbance in the placebo group.

Although the mechanism of action of COX-2 inhibitors predicts a lack of interference with platelet and coagulation factors, a small (5%-10%) potentiation of warfarin effect has been measured in volunteers given rofecoxib, possibly related to an increased plasma concentration of the R(+) warfarin enantiomer. In addition, rofecoxib is highly protein bound and may inhibit warfarin binding to plasma protein, resulting in higher free warfarin levels and increased INR values. Our findings of no significant change in the INR or PT when 50 mg of rofecoxib is coadministered with warfarin are consistent with the previous observations of Reuben et al and suggest that these pharmacodynamic effects are probably not clinically important in most patients.

Both laboratory and clinical data suggest that up-regulation of COX-2 plays a role in postoperative nociception and that COX-2 inhibition at the spinal level may be a key factor for efficacy of an NSAID administered prior to surgery. To our knowledge this is the first reported documentation of CSF concentrations of a selective COX-2 inhibitor after oral administration in humans. These findings do not represent steady-state measurements, which could result in greater CSF penetration of rofecoxib (as shown in our previous animal studies). The importance of our findings is that increased plasma levels of rofecoxib at the start of surgery are correlated with decreased epidural analgesic consumption in the immediate postoperative period. The mean plasma concentrations measured after 2 oral (50 mg) doses of rofecoxib are consistent with values reported after other dosing regimens.

In summary, this study validates the efficacy of perioperative use of rofecoxib to reduce postoperative pain and opioid consumption after major orthopedic surgery. Our findings indicate that continuation of COX-2 inhibition during the postoperative and rehabilitative phases after TKA has important outcome benefits, including reduced PONV and shorter time in physical therapy to achieve effective joint range of motion.
CYCLOOXYGENASE 2 INHIBITOR AFTER KNEE REPLACEMENT

Analysis and interpretation of data: Buwanand, Kroin, Tuman. Drafting of the manuscript: Buwanand, Kroin, Tuman. Critical revision of the manuscript for important intellectual content: Buwanand, Kroin, Tuman, Lubenow, Elmofty, Moric, Rosenberg. Statistical expertise: Kroin, Moric. Obtained funding: Buwanand. Administrative, technical, or material support: Buwanand, Kroin, Tuman, Lubenow, Elmofty, Rosenberg. Study supervision: Buwanand.

Funding/Support: This was an investigator-initiated research study, supported by a medical school grant (MSGP 240) from Merck and Co to the Department of Anesthesiology, Rush Medical College, Chicago, Ill.

Role of the Sponsor: Merck Co, the manufacturer and provider of rofecoxib and placebo used in this study, was not involved in protocol development, data collection and management, statistical analysis, or manuscript preparation. The authors have no affiliations or financial ties with Merck and Co, apart from obtaining the research funding for this study for the Department of Anesthesiology.

Disclosures: Buwanand received research approval from the US Food and Drug Administration for preoperative administration of rofecoxib (Investigational New Drug application No. 61,387).

Acknowledgments: We thank Sarah Youseff, MD, and the Acute Pain Service nurses Minna Masor, RN, BSN, and Jeanne Casadont, RN, BSN, for assistance with monitoring and conducting the protocol for epidural management. We express gratitude to Mitchell Sheinkop, MD, Richard Berger, MD, and Regina Barden, RN, BSN, for assistance in the enrollment of patients in this trial. We also extend appreciation to Pauline Luk of Merck Frosst Canada for the rofecoxib assays.

REFERENCES