Preoperative Rofecoxib Oral Suspension as an Analgesic Adjunct After Lower Abdominal Surgery: The Effects on Effort-Dependent Pain and Pulmonary Function

Raymond S. Sinatra, MD, PhD, Qiheng J. Shen, MD, Thomas Halaszynski, MD, Martha A. Luther, MPH, and Yasser Shaheen, MD

Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

Rofecoxib is a selective cyclooxygenase-2 inhibitor that reduces pain and inflammation without inhibiting platelet function. We examined its effects on effort-dependent pain, postoperative morphine requirements, and pulmonary function in 48 patients recovering from open abdominal surgery. Spirometric measurement of forced expiratory volume in 1 second and vital capacity (FVC) were assessed preoperatively. One hour before the induction of a standardized general anesthetic, patients were given either placebo oral suspension (Group A), or rofecoxib oral suspension (25 mg [Group B] or 50 mg [Group C]) in a double-blinded manner. Postoperative pain control was provided with IV morphine in the postanesthesia care unit and IV-patient-controlled analgesia morphine on the patient care unit. Morphine dose, pain intensity at rest, and pain after respiratory effort (postoperative spirometry) were assessed at 12 and 24 h after study drug administration. The patient-controlled analgesia morphine dose at 24 h was reduced 44% in Group B (30.3 ± 17.5 mg) and 59% in Group C (22.1 ± 16.5 mg) versus Group A (53.7 ± 31.1 mg); P < 0.01 (A versus B). At 12 h, pain scores at rest and after spirometry were lower in Groups B and C than in A (P < 0.05). At 24 h, resting pain scores were lowest in Group C (P < 0.05). Twelve-hour FVC was best preserved in Group C (P < 0.03). There were no inter-group differences in adverse effects or perioperative blood loss. Rofecoxib oral suspension provided a morphine-sparing effect, as well as improvements in pain control and 12-h FVC in patients recovering from open abdominal surgery.

Balanced analgesic techniques that include non-steroidal antiinflammatory drugs (NSAIDs) as adjuncts to opioid analgesics have been shown to reduce effort-dependent pain and improve postsurgical functionality (10–14). The perioperative administration of ketorolac decreased opioid consumption and improved pulmonary function in patients recovering from laparoscopic cholecystectomy (10), and reduced pain scores after ambulation in patients recovering from radical prostatectomy (11). Despite these clinical benefits, ketorolac and other nonselective NSAIDs are generally withheld during the preoperative period because they interfere with platelet function, and increase the risk of surgical bleeding (15,16).

Rofecoxib and other coxibs are distinguished from the broader class of NSAIDs by their selective inhibition of cyclooxygenase (COX)-2 compared with COX-1 (17). This selectivity confers greater perioperative safety because coxibs do not affect platelet aggregation or increase the bleeding time (17,18). Rofecoxib has been approved for the management of acute pain.

Patients recovering from major abdominal surgery tolerate mild-to-moderate discomfort at rest, but are distressed and often incapacitated by severe pain after movement and positioning (1,2). This increase in pain intensity, termed incident or effort-dependent pain, results from stretching or tearing injured tissues, and the release of inflammatory mediators including prostaglandin-E$_2$ (1,3–5). Effort-dependent pain and hyperalgesic muscle spasm (splinting) impairs deep breathing and cough after abdominal and thoracic surgery (1,2,6,7), and may lead to atelectasis and pneumonia, particularly in patients with underlying pulmonary disease (6–9).

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Address correspondence and reprint requests to Dr. Raymond Sinatra, Department of Anesthesiology, Yale University School of Medicine, TMP-3, 333 Cedar St., New Haven, CT 06520-8051. Address e-mail to raymond.sinatra@yale.edu.

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and decreases pain intensity scores and reduces opioid requirements in several orthopedic and dental surgical models (19–22).

This investigation is the first to evaluate rofecoxib oral suspension in patients recovering from major abdominal surgery and to determine its effects on morphine consumption and pain associated with respiratory effort. The hypothesis that reductions in effort-dependent pain may correlate with measurable improvements in pulmonary function was also tested.

Methods

This investigation was approved by the Yale IRB and required written informed consent. Patients 45–65 yr of age, ASA physical status I–II, and scheduled for elective major abdominal surgery were enrolled into this randomized, double-blinded protocol. The primary outcome variables were: 1) The impact of rofecoxib on postoperative opioid analgesic requirements, and 2) rofecoxib’s effect on resting and effort-dependent pain. The secondary outcome variable was postoperative difference from baseline pulmonary function, specifically forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC).

Baseline FEV₁ and FVC were obtained approximately 2 h before surgery using a portable bedside spirometer (Microlab 2000™; MicroMedical Ltd., Kent, UK). Baseline and postoperative FVC and FEV₁ were measured in patients seated in the full upright position. Patients were instructed, and then given two opportunities to use the device. The best attempt was selected.

One hour before anesthetic induction, patients received a single 10-mL oral dose of study medication. Group A (placebo) received 10 mL of placebo oral suspension; Group B (rofecoxib 25 mg) received 5 mL (25 mg) of rofecoxib oral suspension plus 5 mL of placebo suspension; Group C (rofecoxib 50 mg) received 10 mL (50 mg) of rofecoxib oral suspension. Active and placebo oral suspensions were supplied by Merck and Company Inc., Whitehouse Station, NJ, dispensed by the Yale Investigational Pharmacy, and were similar in color and taste.

Patients received a standardized general anesthetic that included midazolam (2 mg) and propofol for induction, and isoflurane, fentanyl, and morphine for maintenance. Intraoperative fentanyl and morphine dose was limited to 5 μg/kg and 0.1 mg/kg, respectively, for scheduled 2- to 3-h abdominal procedures.

Upon arrival to the postanesthesia care unit (PACU), IV boluses of morphine were titrated to achieve patient comfort. A 4-point verbal rating scale score in which 0 = none, 1 = mild, 2 = moderate, and 3 = severe pain was used to assess baseline pain intensity before initiation of IV-patient-controlled analgesia (PCA) with morphine. The PCA device (LifeCare™ PCA; Abbott Medical Products, Chicago, IL) was programmed to provide a 1-mg bolus dose with a lockout interval of 6 min and a 4-h limit of 30 mg.

After discharge to the surgical care unit, the morphine bolus dose could be increased by a member of the investigative team to 1.5 mg for inadequate analgesia, or decreased to 0.5 mg to reduce the severity of adverse effects such as nausea or sedation. Cumulative IV-PCA morphine dose at 12 and 24 h after the administration of study drug and total morphine dose (which included intraoperative, PACU, and 24-h IV-PCA dose), were recorded.

Pain intensity at rest and after respiratory effort were measured at 12 and 24 h after the administration of study drug using a 100-mm visual analog pain scale, anchored with 0 = no pain and 100 = worst pain. Resting pain scores were measured before spirometric assessment of pulmonary volumes with patients lying supine. Effort-dependent pain scores were taken immediately after measurement of FEV₁ and FVC.

Safety assessments included vital signs (the number of patients experiencing clinically significant hypotension and/or tachycardia, oxygen saturation <90%, and respiratory rate <10 breaths/min) and perioperative blood loss. Intraoperative blood loss was estimated and charted by the anesthesiology team and included the amount collected in suction containers and on surgical sponges. Change from baseline hematocrit was calculated by subtracting the hematocrit measured 24 h after surgery from the baseline hematocrit. Opioid-associated adverse events including the number of patients requiring antiemetics (ondansetron 4 mg) for treatment of moderate-to-severe nausea and vomiting, and the number of patients with delayed time until return of bowel function was assessed. Return of bowel function represented the time after surgery when bowel sounds were first documented by surgical staff.

Before initiating the study, power analysis was performed to determine the number of patients necessary to avoid Type II errors in regard to the primary efficacy measurement: reduction in opioid dose. Based on prior evaluations of rofecoxib sparing of IV-PCA morphine and oral opioids (20,22), it was determined that in order to detect a 30% reduction in opioid consumption at the 0.05% level of significance, with a power of 0.6, a minimum of 16 patients were required in each group.

Data were analyzed using repeated-measures analysis of variance and Tukey studentized range tests. Patient demographics were tested using χ² analysis. Pain intensity scores, reduction from baseline pulmonary function, and change from baseline hematocrit were analyzed using paired t-tests. A value of P < 0.05 was considered significant. Data were presented in
tabular form as mean ± sd, and as graphs depicting mean, median, and 25%–75% range.

Results

Fifty patients were entered into the trial. One patient withdrew consent, and another refused IV-PCA, so that 48 patients completed the protocol. Patients randomized included those recovering from abdominal hysterectomy, radical prostatectomy, and simple colectomy, with midline incisions not extending above the tenth thoracic dermatome. Surgical procedures were evenly distributed between treatment groups (Table 1). There were no inter-group differences in patient demographics, duration of surgery, intraoperative and PACU opioid dose, and pain intensity before initiation of IV-PCA in PACU (Table 1). IV-PCA morphine bolus dose was adjusted in 5 patients; 2 from Group A and 1 in Group B requested a dose increase to 1.5 mg whereas 1 patient in Group A and 1 in C required a dose reduction to 0.5 mg.

Patients treated with rofecoxib oral suspension required less morphine than those randomized to receive placebo (Table 2). Total morphine dose averaged 68.3 mg in Group A, and was reduced to 45 mg (34% reduction) in Group B and 33.2 mg (51% reduction) in Group C; P < 0.05 (A versus B), P < 0.01 (A versus C). Cumulative IV-PCA morphine dose was reduced by 44% in Group B and by 59% in Group C; P < 0.05 (A versus B), P < 0.01 (A versus C). At 24 h, only 5 of 16 patients randomized to Group C required >30 mg PCA morphine (equivalent to 1 PCA syringe), as compared with 9 of 16 in Group B and 13 of 16 patients in Group A (P < 0.05; A versus C).

At the 12-h observation interval, visual analog pain scale measurements of resting pain were significantly reduced in rofecoxib-treated groups; P < 0.05 (Fig. 1). Pain scores assessed after respiratory effort at 12 h were also lower; P < 0.05 (A versus B), P < 0.01 (A versus C). At 24 h, resting pain scores were lowest in patients assigned to Group C (P < 0.05). However, inter-group differences in pain intensity after respiratory effort were not observed.

When compared with baseline values, FVC and FEV₁ measured at 12 and 24 h were decreased in all treatment groups (Fig. 2). At 12 h, a 33% reduction from baseline FVC was measured in Group A, a 22% reduction in Group B, and a 16% reduction in Group C (P < 0.03; A versus C). At 12 h, reduction from baseline FEV₁ (liters) was largest in Group A and smallest in Group C; however, differences did not show statistical significance (P = 0.08; A versus C). At 24 h, reduction from baseline FVC in Group A and reductions from baseline FEV₁ measured in all treatment groups were less pronounced than values recorded at 12 h. Inter-group differences in terms of percent reduction from baseline were not observed.

Alterations in perioperative hemodynamics, reductions of either postoperative respiratory rate or oxygen saturation were not observed. There were no inter-group differences in the number of patients requiring ondansetron for moderate-to-severe nausea/vomiting (Table 3). Time until return of bowel sounds was similar in all treatment groups, as was estimated intraoperative blood loss and reduction from baseline hematocrit (Table 3).

Discussion

Preoperative administration of the selective COX-2 inhibitor, rofecoxib, reduced morphine requirements in patients recovering from major abdominal surgery. This morphine-sparing effect was observed throughout the 24-hour study period and was dose-dependent, with the largest reduction in patients receiving rofecoxib 50 mg. Coxibs have been shown to reduce the need for opioid analgesics in several postsurgical models (19–22). However, in an earlier evaluation of patients recovering from radical prostatectomy, preoperative administration of rofecoxib 50 mg did not influence IV-PCA morphine consumption (23). This finding contrasts with the reduced morphine consumption noted in the present investigation, and may be related to differences in study design. We evaluated pain intensity after respiratory effort as well as pain at rest, limited intraoperative opioid administration, and used rofecoxib oral suspension rather than rofecoxib tablets. The oral suspension is rapidly absorbed and has an onset of effect within 35 minutes (18).

Intraabdominal surgery is often associated with reductions in postoperative lung volumes, a decreased ability to cough and clear secretions, and pulmonary morbidity that can prolong hospital stay (2,6–9,24). Patients attempting to cough or perform a vital capacity maneuver generally experience increased discomfort as they inhale deeply and forcefully exhale (7–9). For this reason, spirometric measurement of FVC and FEV₁ was used to quantify whether reductions in respiratory effort-dependent pain correlated with measurable improvements in pulmonary volume (2,24).

At 12 hours, FVC in patients treated with placebo was reduced by 1 L. This 33% reduction is similar to that previously reported in patients treated with opioid analgesics after abdominal surgery (6–9,24). Tsang and Brush (25) evaluated the effects of IV-PCA and nurse-administered boluses of morphine on postsurgical pain intensity and pulmonary function. Patients in each group reported mild-to-moderate pain at rest, but all reported increased discomfort after deep breathing, and experienced significant reductions in FVC and peak inspiratory flow. These findings and those of the present study suggest that IV-PCA morphine by itself may be less effective in compensating
Figure 1. Visual analog pain scale (VAPS) scores at rest and after respiratory effort (spirometric assessment of forced vital capacity) at 12 and 24 h after the administration of study medication. A = placebo, B = rofecoxib 25 mg, C = rofecoxib 50 mg. Box and whisker plots: box (25% and 75% values), line in box (mean), + (median), and whiskers (5%–95% values). *Significant difference versus Group A, \( P < 0.05 \); **Significant difference versus Group A, \( P < 0.01 \).

Figure 2. Reduction from baseline forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV\(_1\)) at 12 and 24 h after the administration of study medication. A = placebo, B = rofecoxib 25 mg, C = rofecoxib 50 mg. Box and whisker plots: box (25% and 75% values), line in box (mean), + (median), and whiskers (5%–95% values). *Significant difference Group C versus Group A, \( P < 0.03 \).

Table 1. Patient Demographics and Intraoperative Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (placebo) ((n = 16))</th>
<th>Group B (rofecoxib 25 mg) ((n = 16))</th>
<th>Group C (rofecoxib 50 mg) ((n = 16))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.8 ± 9.8</td>
<td>50.1 ± 13.3</td>
<td>45.6 ± 11.6</td>
<td>0.38</td>
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<td>Sex (male:female)</td>
<td>(7:10)</td>
<td>(5:11)</td>
<td>(7:10)</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.5 ± 17.5</td>
<td>80.9 ± 19.4</td>
<td>75 ± 14.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>161.3 ± 44.5</td>
<td>143.2 ± 34.0</td>
<td>155.1 ± 54.7</td>
<td>0.87</td>
</tr>
<tr>
<td>Abdominal hysterectomy ((n))</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Radical prostatectomy ((n))</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Colectomy ((n))</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Other abdominal surgery ((n))</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Verbal pain score in PACU</td>
<td>2.3 ± 0.9</td>
<td>2.0 ± 0.9</td>
<td>2.1 ± 0.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Intraoperative fentanyl ((\mu g))</td>
<td>304 ± 125</td>
<td>245 ± 86</td>
<td>251 ± 113</td>
<td>0.58</td>
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<tr>
<td>Intraoperative morphine (mg)</td>
<td>7.9 ± 4.0</td>
<td>8.3 ± 5.4</td>
<td>6.5 ± 5.0</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Values represent mean ± sd.
PACU = postanesthesia care unit.

Table 2. Postoperative Opioid Dose

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (placebo) ((n = 16))</th>
<th>Group B (rofecoxib 25 mg) ((n = 16))</th>
<th>Group C (rofecoxib 50 mg) ((n = 16))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACU morphine (mg)</td>
<td>6.7 ± 5.0</td>
<td>6.4 ± 4.3</td>
<td>5.6 ± 3.4</td>
<td>0.76</td>
</tr>
<tr>
<td>12-h PCA morphine (mg)</td>
<td>25.6 ± 15.1</td>
<td>14.9 ± 9.4*</td>
<td>10.2 ± 8.0*</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>24-h PCA morphine (mg)</td>
<td>53.7 ± 31.1</td>
<td>30.3 ± 17.5*</td>
<td>22.1 ± 16.5*</td>
<td>&lt;0.05*, &lt;0.01†</td>
</tr>
<tr>
<td>Total morphine dose (mg)</td>
<td>68.3 ± 25.2</td>
<td>45.0 ± 14.1*</td>
<td>33.2 ± 14.2†</td>
<td>&lt;0.05*, &lt;0.01†</td>
</tr>
</tbody>
</table>

Values represent mean ± sd.
Twelve- and 24-h IV-patient-controlled analgesia (PCA) morphine dose represents cumulative self-administered dose measured at those intervals. Total morphine dose represents the sum of the intraoperative dose, postanesthesia care unit (PACU) dose, and 24-h IV-PCA dose.
*Significant difference Group B or C versus Group A.
†Significant difference Group C versus Group A.
treatment group. Preservation of 12-hour FEV\textsubscript{1} scores and FVC were noted in the 50-mg rofecoxib group. In postoperative 12-hour effort-dependent pain period. In the present investigation, similar improvements in pain intensity and had greater preservation of baseline FEV\textsubscript{1} and FVC during the early postoperative period. In the present investigation, similar improvements in postoperative 12-hour effort-dependent pain scores and FVC were noted in the 50-mg rofecoxib treatment group. Preservation of 12-hour FEV\textsubscript{1} may have also achieved statistical significance had the study been adequately powered to detect differences in this aspect of pulmonary function. Improvements in pain control and morphine-sparing effects noted with rofecoxib are likely the result of perioperative COX-2 inhibition. Reductions in prostaglandin synthesis would be expected to diminish nociceptor sensitization and inflammatory responses that normally accompany movement and stretching of injured tissues (3,10,17,28).

Benefits associated with rofecoxib were not maintained beyond the 12-hour observation interval. This limitation of effect may be related to several factors: 1) the antiinflammatory and additive analgesic effect of a single dose of rofecoxib may have decreased to the point that it was clinically ineffective at the 24-hour observation interval. In this regard, the ability of rofecoxib 50 mg to reduce pain intensity after orthopedic lumbar fusion was limited to 16 hours, although its morphine-sparing effect continued for 24 hours (22). 2) Patients in the control group may have self-administered adequate amounts of morphine by 24 hours to minimize effort-dependent pain. 3) In this lower abdominal model, pain intensity after respiratory effort, and its impact of pulmonary volume, was not severe or prolonged to distinguish benefits at 24 hours.

Rofecoxib and other COX-2 inhibitors are not specifically approved for use before surgery (18); however, in the present investigation, preoperative administration was necessary because the majority of patients recovering from abdominal exploration and exposure to general anesthesia are unable to take oral medications. A second reason for using a preoperative dosing paradigm was to gain a “preemptive analgesic” effect (28,29). Although this concept remains controversial (30), pretreatment with coxibs (31) would be expected to prevent COX-2 up-regulation and minimize release of prostaglandin-E\textsubscript{2} and other inflammatory mediators during intraoperative dissection and surgical manipulation. In a dose-timing comparison study, patients treated with rofecoxib 50 mg 1 hour before surgery reported significant improvements in pain relief and reductions in postoperative opioid consumption than others given the same dose after surgery (21).

The present investigation, whereas focusing on morphine consumption and pain intensity, lacked the power necessary to detect inter-group differences in postsurgical opioid morbidity, and coxib effects on hemostasis. Despite reductions in morphine exposure, patients treated with rofecoxib did not benefit from reductions in need to treat moderate-to-severe nausea/vomiting or experience a more rapid return of bowel sounds. This observation was made during the specified postoperative time period in which the patients were being followed (24 hours) and it should also be appreciated that opioids are only one factor of several to consider when measuring postoperative nausea and vomiting. In agreement with prior investigations, preoperative administration of rofecoxib did not result in a greater reduction in postsurgical hematocrit (21,22,29).

In conclusion, preoperative administration of rofecoxib oral suspension reduced morphine requirements with greater preservation of baseline vital capacity 12 hours postoperatively in patients recovering from open abdominal surgery. The hypothesis that coxibs may reduce the magnitude of these events should be further tested in more invasive surgical settings, or in patients with underlying lung disease where preservation of pulmonary function may have greater significance (8,9).

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