

# The Cyclooxygenase-2-Specific Inhibitor Parecoxib Sodium Is as Effective as 12 mg of Morphine Administered Intramuscularly for Treating Pain After Gynecologic Laparotomy Surgery

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Parecoxib sodium, the injectable prodrug of valdecoxib, is a cyclooxygenase-2-specific inhibitor that is effective in the treatment of postoperative pain. In this randomized, double-blind, placebo-controlled study, we compared the efficacy of a single dose of parecoxib sodium 40 mg IM with single doses of morphine 6 and 12 mg IM in treating postoperative pain after gynecologic surgery requiring a laparotomy incision. By nearly all efficacy measures (including total pain relief and patient's global evaluation of study medication), parecoxib sodium 40 mg IM demonstrated pain relief and a decrease in pain intensity that was statistically

similar to that with morphine 12 mg IM and superior to that with morphine 6 mg IM. Parecoxib sodium 40 mg IM-treated patients also demonstrated a longer time to use of rescue medication than patients treated with both morphine doses, and this dose provided sustained pain relief over the 12-h study period. The incidence of adverse events in the active treatment groups was similar to that observed with placebo. Parecoxib sodium, 40 mg IM, has been shown to be as effective as clinically relevant doses of morphine in patients after gynecologic laparotomy surgery.

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Opioids and nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used analgesics for the treatment of postoperative pain (1,2). Opioids are effective analgesics; however, they have been shown to be associated with adverse events (AEs) such as respiratory depression, dizziness, somnolence, nausea, and vomiting, and these delay recovery after surgery (3). A multimodal drug treatment strategy that combines two or more analgesics with different modes of action has been used to reduce the requirement for opioids and is now an accepted method of treating pain after surgery (4). This strategy takes advantage of the decrease in side effects associated with any single drug in addition to providing improved analgesic efficacy.

Nonspecific NSAIDs, which inhibit both cyclooxygenase (COX)-1 and COX-2, are also effective in the treatment of postoperative pain and have been used to treat many painful conditions and in multimodal therapy. The AEs associated with nonspecific NSAIDs are due to inhibition of COX-1, whereas their antiinflammatory and analgesic properties are mediated through the action of COX-2. Nonspecific NSAID-associated AEs include blockade of platelet function, which in turn increases the risk of postoperative bleeding, and gastrointestinal (GI) toxicity (5,6). In contrast, COX-2-specific inhibitors are effective antiinflammatory analgesics that do not block platelet inhibition. COX-2-specific inhibitors also greatly reduce the risk of GI side effects that are characteristic of nonspecific NSAIDs.

Parecoxib sodium is an injectable prodrug formulation of the orally administered COX-2-specific inhibitor valdecoxib, which is available in more than 20 countries for management of postoperative pain. Parecoxib sodium has been shown to be effective for the treatment of postoperative pain after oral, orthopedic joint replacement, and gynecologic surgery; it has a

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rapid onset and long duration of action (7–9). A single dose of parecoxib sodium 40 mg has been shown in controlled studies to provide superior analgesic efficacy and a longer duration of action compared with a single dose of morphine 4 mg (7,10). Parecoxib sodium 40 mg also has significant opioid-sparing effects of up to 39% as part of a multimodal treatment strategy in orthopedic surgery patients (11,12). As a consequence, patients receiving parecoxib sodium plus morphine discontinued patient-controlled analgesia (PCA) morphine more rapidly and reported improved global evaluation of study medication scores compared with patients receiving morphine alone (11,12).

Although parecoxib sodium, 40 mg, has previously been shown to provide superior analgesic efficacy to morphine 4 mg IV, we decided to examine the efficacy of parecoxib 40 mg against larger doses of morphine that might be more clinically relevant. Therefore, we evaluated the analgesic efficacy of a single dose of parecoxib sodium, 40 mg IM, compared with single doses of morphine, 6 and 12 mg IM, and placebo for the treatment of pain after gynecologic surgery requiring a standard laparotomy incision.

## Methods

This study was a multicenter, randomized, double-blind, placebo-controlled, single-dose trial to evaluate the efficacy of parecoxib sodium 40 mg IM compared with morphine 6 and 12 mg IM after gynecologic surgery. All eligible patients were women who were not lactating, who were of legal age of consent, and who had undergone elective lower abdominal gynecologic surgery through a standard transverse or lower midline incision under general anesthesia. Patients were treated for pain immediately after surgery by using morphine delivered by standard PCA, which was continued until the morning after surgery. If, between 30 min and 6 h after discontinuation of PCA the morning after surgery, patients developed a pain intensity that was moderate to severe on a four-point categorical scale (none, mild, moderate, or severe) and was  $\geq 50$  mm on the visual analog scale (VAS; 0–100 mm) (after performing an aggravated “log roll” movement), they were randomized to receive one of the following IM treatments: parecoxib sodium 40 mg, morphine 6 mg, morphine 12 mg, or placebo. Patient randomization was determined with a random-number generator computed by the sponsor.

Eligible patients underwent a physical examination, including vital signs and clinical laboratory assessment, during a 14-day pretreatment period. The study was approved by an IRB at all sites and was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients were excluded from the study if they were scheduled to undergo any other surgical procedure that was expected to produce more pain than standard elective gynecologic surgery with a laparotomy incision. Patients were excluded if they took medications that might interfere with pain assessments, including other analgesics, tricyclic antidepressant drugs (new starts), NSAIDs, or corticosteroids, during the 6 h preceding surgery. Midazolam was also allowed as a preoperative medication.

In the postsurgical period, rescue medication was permitted at any time when requested by the patient. Patients who took rescue medication before the completion of the 12-h study period completed no additional pain measurements, although they remained at the study site for the entire 12-h study period.

During the 12-h treatment period, pain-intensity assessments (categorical scale and VAS) were performed at 0 h (baseline assessment taken immediately before receiving study medication and after performing an aggravated movement), 30 min, and 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h or until rescue medication was requested. Pain intensity was evaluated on a 0- to 100-mm VAS, where 0 mm was no pain and 100 mm was the worst imaginable pain, and the categorical pain-intensity assessment used a four-point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). Pain-intensity difference (PID) was calculated by subtracting patients' pain-intensity scores at each time point from their baseline pain-intensity scores. Pain relief was assessed with a five-point categorical scale, where 0 = no pain relief, 1 = a little, 2 = some, 3 = a lot, and 4 = complete pain relief. Patients completed a global evaluation of study medication at the last assessment period (12 h after the administration of study medication) or immediately before rescue medication on a scale of 1 to 4, where 1 = poor, 2 = fair, 3 = good, and 4 = excellent.

Efficacy was assessed by recording the time-weighted sum of total pain relief scores (TOTPAR) through the first 4, 6, 8, and 12 h after the administration of study medication (TOTPAR-4, -6, -8, and -12); PID; time to rescue medication; the proportion of patients who required rescue medication; and the patient's global evaluation of study medication. General clinical safety was monitored by the incidence of treatment-emergent AEs, serious AEs, physical examination, vital signs, and clinical laboratory analysis.

The sample size was calculated by using TOTPAR-8 for the comparison of parecoxib sodium 40 mg with each dose of morphine (6 and 12 mg). According to the results of a previous post-gynecologic surgery pain study, a mean TOTPAR-8 of 15.0 in the parecoxib sodium 40 mg group was assumed. A sample size of 62 patients per treatment group was required to detect a difference between parecoxib sodium 40 mg and each dose of morphine (6 and 12 mg) of at least 4.5 U

with a power of at least 80% and a two-sided significance of 0.025 (on a two-sided test adjusted for two comparisons).

Baseline characteristics were compared across treatment groups by using two-way analysis of variance with treatment and center as factors or by using the Cochran-Mantel-Haenszel test for categorical variables. All efficacy analyses were performed on the modified intention-to-treat (ITT) population. The ITT cohort consisted of all patients who completed the surgery and received study medication but did not take rescue medication before the 1-h pain assessment, did not take a prohibited medication, and did not have a protocol violation. All patients who received a dose of study medication were included in the safety analysis.

The "last observation carried forward" approach was used in the efficacy analyses to account for missing pain-intensity and pain-relief values or for data missing as a result of patients taking rescue medication or withdrawing from the study. The baseline scores for PID and pain relief were, by definition, 0. The time-specific variables PID and pain relief and the time-weighted variable TOTPAR were analyzed with a general linear model with treatment and center as factors. Time to rescue medication was calculated by subtracting the time rescue medication was requested from the time the dose of study drug was taken, and data were analyzed with Kaplan-Meier survival estimates. The method of Simon and Lee (13) was used to calculate 95% confidence intervals for the median time to events. The patient's global evaluation of study medication at the end of the study was analyzed with the Cochran-Mantel-Haenszel test, stratified by center. The incidence of treatment-emergent AEs was compared between groups by using Fisher's exact test.

## Results

A total of 264 patients were randomized; 70 patients each were randomized to receive placebo or morphine 6 mg, and 62 patients each were randomized to receive morphine 12 mg or parecoxib sodium 40 mg. Baseline demographics and baseline pain-intensity scores (categorical scale or VAS) were not significantly different across the treatment groups (Table 1). Approximately 40% of patients in each treatment group reported severe pain at the time of randomization, and most reported moderate pain at baseline.

Fourteen patients were excluded from the ITT population: five in the placebo group, two in the morphine 6 mg group, three in the morphine 12 mg group, and four in the parecoxib sodium 40 mg group. The reasons for exclusion were protocol violation, failed inclusion and exclusion criteria, rescue medication taken

before the 1-h assessment, missing consecutive pain relief scores, and study medication administered 12 h after PCA was stopped.

Treatment with parecoxib sodium 40 mg provided significantly greater pain relief, as assessed with mean time-weighted TOTPAR, than morphine 6 or 12 mg or placebo at nearly all times measured (Table 2). At 8 h, the TOTPAR-8 score in the parecoxib sodium 40 mg group (17.0) was significantly higher than the mean scores in the morphine 12 mg (13.5), morphine 6 mg (11.9), and placebo (6.9) groups ( $P \leq 0.02$ ). In addition, the TOTPAR-4 score in the parecoxib sodium 40 mg group (9.0) was significantly greater compared with the mean scores in the placebo (4.4) and morphine 6 mg (7.0) groups ( $P \leq 0.01$ ), although it was not significantly greater than in the morphine 12 mg group (8.1).

Parecoxib sodium 40 mg treatment provided a decrease in pain intensity that was similar to that with morphine 12 mg and superior to that with morphine 6 mg (Fig. 1). Compared with morphine 6 mg, treatment with parecoxib sodium 40 mg provided significantly better PID scores (VAS [Fig. 1] and categorical scale) within 4 h of dosing, and these were maintained over the 12-h study period ( $P < 0.001$ ). Furthermore, compared with morphine 12 mg, parecoxib sodium 40 mg provided greater improvements in mean PID scores (VAS) from 4 to 10 h ( $P < 0.001$ ), whereas the categorical scale analysis showed parecoxib sodium 40 mg to be numerically different from morphine 12 mg IM.

The median time to rescue medication was longer for patients treated with parecoxib sodium 40 mg (5 h 53 min) than for patients treated with placebo (2 h 14 min), morphine 6 mg (3 h 59 min), or morphine 12 mg (4 h 22 min) (Fig. 2). The proportion of patients receiving rescue medication over the 12-h study period was similar in each of the active treatment groups: morphine 6 mg (88%), morphine 12 mg (88%), and parecoxib sodium 40 mg (79%).

Patients receiving either parecoxib sodium 40 mg or morphine 12 mg reported significantly higher patient's global evaluation scores with their study medication than those receiving morphine 6 mg or placebo ( $P < 0.01$ ) (Fig. 3). The proportion of patients who rated their treatment as "excellent" was larger in the parecoxib sodium 40 mg group (47%) than in the morphine 12 mg (33%), morphine 6 mg (23%), and placebo (11%) groups.

The incidence of AEs reported by at least 5% of patients in any treatment group is summarized in Table 3. There were no statistically significant differences in the incidences of AEs among treatment groups, except for headache, which was significantly less frequent in the parecoxib sodium 40 mg group. Most AEs were typical of the postoperative setting. Overall, 28 (40.0%) patients in the placebo group, 19 (30.6%) patients in the parecoxib

**Table 1.** Patient Characteristics and Baseline Variables

Variable	Placebo ( <i>n</i> = 70)	Morphine 6 mg IM ( <i>n</i> = 70)	Morphine 12 mg IM ( <i>n</i> = 62)	Parecoxib sodium 40 mg IM ( <i>n</i> = 62)
Mean age (yr)	44.2	46.2	43.6	44.3
Racial or ethnic group, <i>n</i> (%)				
Caucasian	46 (66)	47 (67)	42 (68)	42 (68)
African American	20 (29)	20 (29)	15 (24)	16 (26)
Asian	1 (1)	1 (1)	1 (2)	1 (2)
Hispanic	3 (4)	2 (3)	4 (6)	3 (5)
Height (cm)				
Mean	163.1	164.4	162.2	163
Range	77.0–182.9	127.0–182.9	149.9–188.0	149.9–177.8
Weight (kg)				
Mean	81.7	84.6	79.1	79.1
Range	52.2–122.7	47.6–149.0	45.4–138.7	47.2–143.2
Pain intensity <sup>a</sup> (categorical), <i>n</i> (%)				
Moderate	40 (57)	41 (59)	37 (60)	38 (61)
Severe	30 (43)	29 (41)	25 (40)	24 (39)
Pain intensity <sup>a</sup> (VAS)				
Mean	68.5	68.9	66.9	65.8
Range	50–100	50–100	42–100	50–100

VAS = visual analog scale.

<sup>a</sup> Pain intensity was measured at Time 0, immediately before receiving study medications and after performing an aggravated movement.**Table 2.** Time-Weighted Sum of Pain Relief<sup>a</sup> at 4, 6, 8, and 12 h After Treatment in the Intention-to-Treat Population

Posttreatment time	Placebo ( <i>n</i> = 70)	Morphine 6 mg ( <i>n</i> = 70)	Morphine 12 mg ( <i>n</i> = 62)	Parecoxib sodium 40 mg ( <i>n</i> = 62)
4 h				
<i>n</i>	19	34	39	40
Mean ± SD	4.4 ± 3.8 (C)	7.0 ± 4.1 (B)	8.1 ± 3.6 (AB)	9.0 ± 4.4 (A)
6 h				
<i>n</i>	7	15	17	30
Mean ± SD	5.8 ± 5.5 (C)	9.6 ± 6.0 (B)	11.0 ± 5.7 (AB)	13.3 ± 6.9 (A)
8 h				
<i>n</i>	3	6	8	22
Mean ± SD	6.9 ± 6.9 (C)	11.9 ± 8.0 (B)	13.5 ± 7.7 (B)	17.0 ± 9.2 (A)
12 h				
<i>n</i>	1	2	3	8
Mean ± SD	9.0 ± 9.6 (C)	16.0 ± 11.6 (B)	18.2 ± 11.7 (B)	23.3 ± 13.6 (A)

The overall treatment *P* value was <0.001 at each time point. A, B, C—for pairwise comparisons, treatments with same letter were not significantly different from each other.<sup>a</sup> Mean value over a specified time multiplied by time; i.e., the 4-h value is the mean hourly score from 0 to 4 h multiplied by 4.

sodium 40 mg group, 27 (38.6%) patients in the morphine 6 mg group, and 33 (53.2%) patients in the morphine 12 mg group had AEs that were considered to be related to study medication. Three patients in the morphine 6 mg group, three patients in the morphine 12 mg group, and one patient in the parecoxib sodium 40 mg group withdrew from the study because of treatment-emergent AEs.

In all treatment groups, there were no clinically significant changes from baseline in creatinine values (*P* > 0.2 for parecoxib sodium versus morphine 6 and 12 mg; *P* = 0.1 versus placebo). However, the mean change in blood urea nitrogen in the parecoxib sodium group was significantly less than in the placebo (*P* = 0.008) and morphine 6 mg (*P* = 0.025) groups, but not

the morphine 12 mg group. The mean change from baseline in systolic blood pressure for the parecoxib sodium 40 mg group was decreased by 1–2 mm Hg throughout the study and was statistically significantly different from the other treatment groups. These changes were not considered to be clinically meaningful.

## Discussion

In this study, a single postoperative dose of parecoxib sodium 40 mg IM provided analgesic efficacy that was superior to that with a single dose of morphine 6 mg and was comparable to that with a single dose of morphine

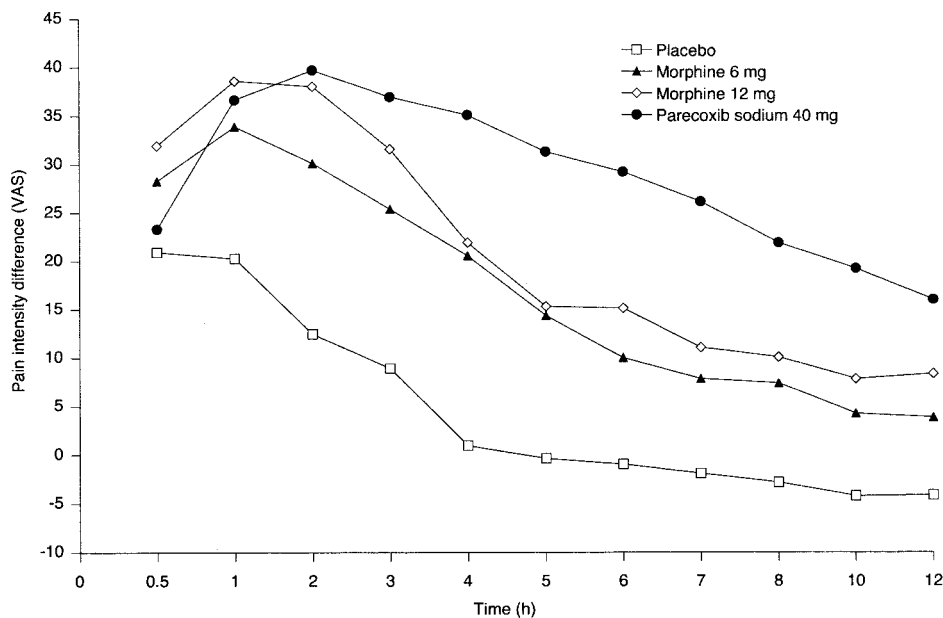


Figure 1. Mean pain-intensity difference scores over time with the visual analog scale (VAS) in the intention-to-treat population.

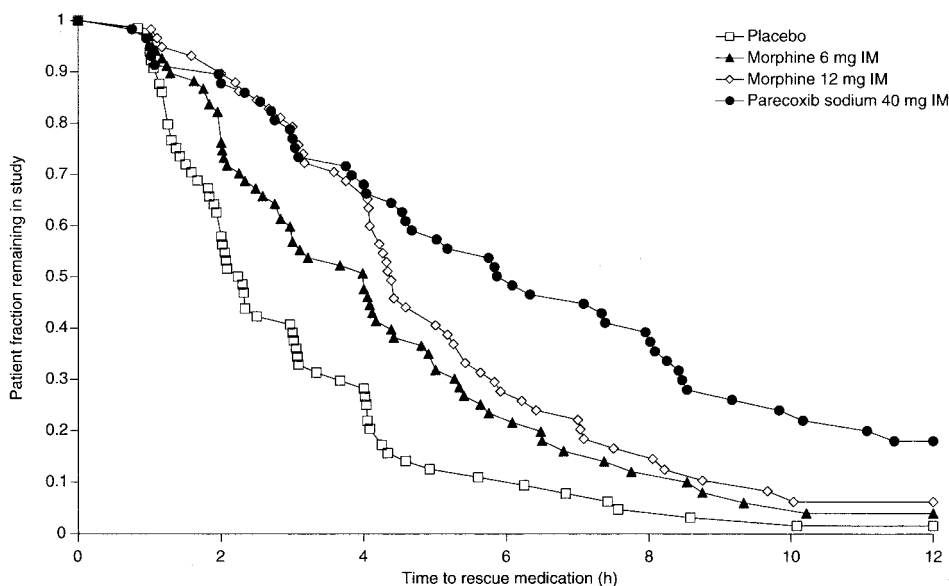


Figure 2. Median time to rescue medication in the intention-to-treat population.

12 mg after gynecologic laparotomy surgery. Within the first four hours of the study, significant improvements in analgesic efficacy were observed with parecoxib sodium 40 mg compared with morphine 6 mg, and similar improvements to morphine 12 mg were also observed. Although the primary efficacy measure was TOTPAR at eight hours, the total-pain relief of parecoxib sodium 40 mg was superior to that of morphine as early as four hours after study drug treatment. At later time points (longer than four hours), significantly greater TOTPAR and PID scores were observed with parecoxib sodium 40 mg treatment compared with morphine 6 and 12 mg. The duration of effect of parecoxib sodium, assessed by median time to rescue medication, in previous studies

has been shown to be in the range of 6–24 hours, depending on the type of surgery (7,10). Because gynecologic laparotomy is a major surgical procedure that results in moderate to severe pain, the duration of effect of parecoxib sodium might be expected to be shorter than for other, less invasive, procedures. The median time to rescue medication of approximately six hours in this study is consistent with previous studies of gynecologic surgery. Furthermore, the time to rescue medication for parecoxib sodium-treated patients was longer than for patients treated with morphine 6 and 12 mg.

In addition to studies that compared the efficacy of parecoxib sodium with that of morphine, studies have also shown that a single dose of parecoxib sodium

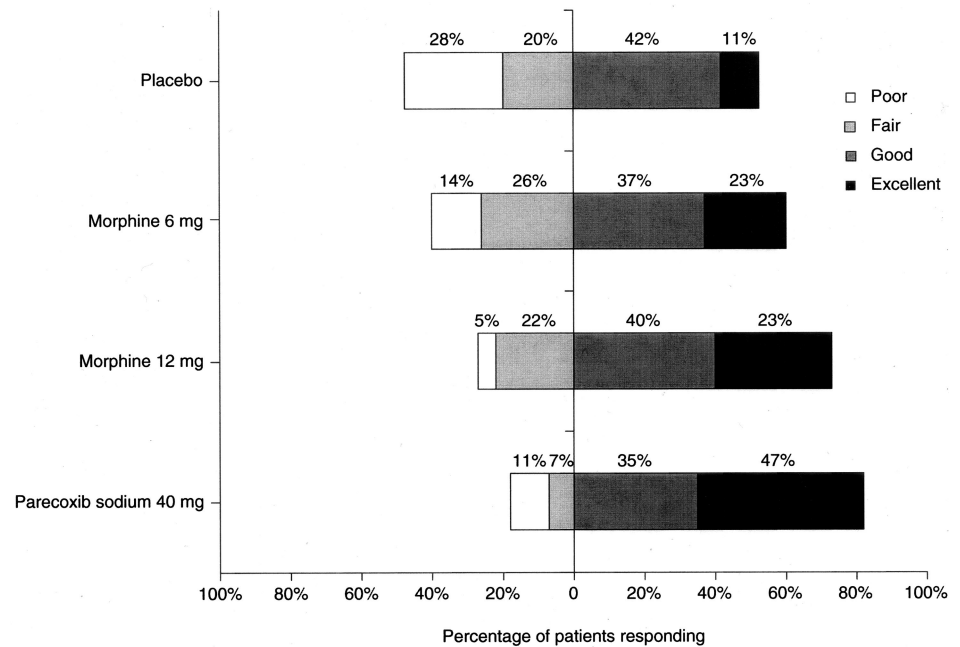


Figure 3. Patient's global evaluation of study medication.

Table 3. Incidence of Adverse Events (AEs) Reported by ≥5% of Patients in Any Treatment Group

AE	Placebo (n = 70)	Morphine 6 mg (n = 70)	Morphine 12 mg (n = 62)	Parecoxib sodium 40 mg (n = 62)
Nausea	19 (27.1)	19 (27.1)	21 (33.9)	11 (17.7)
Vomiting	10 (14.3)	7 (10.0)	10 (16.1)	4 (6.5)
Headache	9 (12.9)	6 (8.6)	8 (12.9)	0 (0.0)
Fever	8 (11.4)	14 (20.0)	13 (21.0)	6 (9.7)
Somnolence	4 (5.7)	5 (7.1)	10 (16.1)	8 (12.9)
Flatulence	2 (2.9)	4 (5.7)	4 (6.5)	5 (8.1)
Pruritus	1 (1.4)	6 (8.6)	6 (9.7)	6 (9.7)
Dizziness	1 (1.4)	2 (2.9)	4 (6.5)	6 (9.7)
Total	41 (58.6)	43 (61.4)	44 (71.0)	36 (58.1)

Data are n (%).

40 mg is at least as effective as single doses of ketorolac 30 and 60 mg in relieving postsurgical pain (7,10,14). Thus, in several studies of varying levels of postoperative pain, parecoxib sodium 40 mg provides analgesic efficacy similar to that with standard-dose opioids and injectable NSAIDs and thus provides physicians with an effective analgesic option. Additionally, as shown in this study, because parecoxib sodium 40 mg provides efficacy similar to that with a larger dose of morphine (12 mg) the day after surgery, parecoxib sodium 40 mg might be used initially in the treatment of postoperative pain, either alone or as part of multimodal therapy, depending on pain severity. Finally, because parecoxib sodium 40 mg in this study showed a longer time to request for rescue medication, this prolonged efficacy may delay patients' request for additional postoperative opioid medication or may prevent the request for opioid medication altogether.

Parecoxib sodium 40 mg was well tolerated in this study. Overall, the incidence of AEs experienced by parecoxib sodium-treated patients was similar to that observed with placebo. Furthermore, there were fewer composite opioid-related GI AEs, such as nausea and vomiting, with parecoxib sodium 40 mg treatment than with morphine 6 and 12 mg. Because a principal concern with opioid use is the high risk of opioid-related side effects such as nausea, vomiting, dizziness, and respiratory depression (15,16), pain-management strategies that reduce the need for postoperative opioids are highly desirable. Because parecoxib sodium by itself is not associated with typical opioid-related side effects, it may have the added benefit of improving patient tolerability when given concomitantly with or after the initiation of opioid therapy.

Patients who received parecoxib sodium 40 mg reported significantly improved global evaluation

scores with their study medication compared with patients who received morphine 6 mg and reported similar scores to patients who received morphine 12 mg. This result is likely due to the combination of effective pain control, a long duration of analgesia, and improved tolerability.

The results from this study support the conclusion that a single dose of parecoxib sodium 40 mg is as effective as a single dose of morphine 12 mg IM given the day after laparotomy surgery. These findings suggest that parecoxib sodium 40 mg can be used successfully in the management of postoperative pain, either alone or as part of multimodal therapy after major surgery. Improved pain scores and an earlier return of bowel function should assist in patient recovery and earlier discharge planning after inpatient surgery.

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