

Efficacy and Safety of Intravenous Parecoxib Sodium in Relieving Acute Postoperative Pain following Gynecologic Laparotomy Surgery

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Background: This study tested the hypothesis that an injectable cyclooxygenase (COX)-2-specific inhibitor will be at least as effective and well tolerated as a COX-nonspecific conventional nonsteroidal antiinflammatory drug (NSAID) by comparing the analgesic efficacy and tolerability of one intravenous dose of parecoxib sodium, an injectable prodrug of the novel COX-2-specific inhibitor, valdecoxib, with ketorolac and placebo in postoperative laparotomy surgery patients. Intravenous morphine, 4 mg, was studied as a positive analgesic control.

Methods: In this multicenter, double-blinded, placebo-controlled study, women experiencing moderate-to-severe pain on the first day after abdominal hysterectomy or myomectomy received one intravenous dose of parecoxib sodium, 20 or 40 mg, ketorolac, 30 mg, morphine, 4 mg, or placebo. Analgesic efficacy and tolerability were evaluated for 24 h postdose or until patients, whose pain was not adequately controlled, opted to receive rescue analgesia.

Results: Two hundred two patients were enrolled. All treatment groups had comparable demographics and baseline pain status. All active treatments had an equally rapid time to onset of analgesia (10–23 min). Overall, each parecoxib sodium dose and ketorolac were significantly superior to morphine and placebo for most measures of analgesic efficacy at most time points, including a significantly longer (two- to threefold) time to rescue analgesia ($P \leq 0.05$). All treatments were well tolerated.

Conclusions: Single intravenous doses of parecoxib sodium, 20 mg and 40 mg, have comparable analgesic effects and are well tolerated after laparotomy surgery. Parecoxib sodium appears to be as effective as intravenous ketorolac, 30 mg, and superior to intravenous morphine, 4 mg.

CONVENTIONAL nonsteroidal antiinflammatory drugs (NSAIDs), widely used for postoperative pain management, are associated with adverse events that limit their clinical utility.^{1,2} Acute NSAID administration increases the risk of upper gastrointestinal (GI) bleeding, acute renal failure, and excessive intra- or postoperative bleeding.^{3–13} Hemorrhagic lesions and ulcers can occur within a few days of conventional NSAID treatment, and patients with coagulation abnormalities or those receiving

antiplatelet agents or anticoagulants are at high risk of NSAID-related hemorrhage.^{7–14} The risk of excessive intra- or postoperative bleeding may preclude the use of NSAIDs during surgical procedures in which optimal hemostasis is critical. The benefits and potential risks of acute NSAID treatment should, therefore, be considered carefully when selecting postoperative analgesic agents.^{1,15} The tolerability and usefulness of opioids are also limited in many patients by adverse effects such as nausea, vomiting and ileus, respiratory depression, and central nervous system effects.¹⁶

The analgesic and antiinflammatory effects of cyclooxygenase (COX)-2-specific inhibitors and conventional NSAIDs are mediated by COX-2 inhibition.^{17–20} Conventional NSAIDs inhibit COX-1, resulting in upper GI and hematologic adverse effects, whereas COX-2-specific inhibitors spare COX-1 at therapeutic concentrations and, therefore, have a superior safety and tolerability profile.^{20–23}

Although the COX-2-specific inhibitors and most conventional NSAIDs are orally administered, injectable formulations are preferred in acutely painful conditions, especially in the perioperative setting, and when patients cannot tolerate oral medication or require rapid analgesia. Ketorolac, which has considerable GI toxicity, is the only injectable conventional NSAID available in the United States, whereas diclofenac, ketoprofen, indomethacin, and acetaminophen (propacetamol) are available in other countries.^{1,24–26}

Parecoxib sodium is a novel, inactive prodrug that when parenterally administered is rapidly converted to the COX-2-specific inhibitor, valdecoxib, which spares COX-1 at therapeutic concentrations.^{27–29} Because the analgesic effect of valdecoxib is not reversible by naloxone, it is unlikely to exhibit the potential for abuse or the adverse effects typical of opioids.^{29,30} Parecoxib sodium, 40 mg, is rapidly acting, comparable in efficacy with a 60-mg intramuscular dose of ketorolac, and nonulcerogenic in healthy elderly subjects.^{28,31–33}

This study evaluated the analgesic efficacy and tolerability of parecoxib sodium to test the hypothesis that it will be at least as effective and well tolerated as an injectable conventional NSAID in managing acute postoperative pain. Single doses of intravenous parecoxib sodium, 20 mg and 40 mg, were compared with placebo, intravenous ketorolac, 30 mg, or intravenous morphine, 4 mg (positive analgesic control) in patients after gynecologic surgery *via* laparotomy.

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Materials and Methods

Written informed consent was provided by all patients before enrollment, and the study was conducted in accordance with Good Clinical Practices. The study was approved by the appropriate Institutional Review Boards and conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

This multicenter, double-blinded, placebo-controlled, parallel group study was conducted in five centers (21–70 patients per center) in the United States (see Appendix). Study subjects were women aged 18–64 yr requiring parenteral analgesia for moderate or severe pain after elective total abdominal hysterectomy or myomectomy, but who were otherwise generally healthy. After surgery, patient-controlled analgesia was provided with morphine sulfate, 0.5–2 mg/dose, or meperidine hydrochloride (Demerol®, Sanofi Pharmaceuticals, Inc., New York, NY), 10–30 mg/dose, with a 10-min lockout between doses. Basal infusions of morphine, 0.5–1.0 mg/h, or meperidine hydrochloride, 10–30 mg/h, were permitted in addition to the patient-controlled doses. Patients continued on patient-controlled analgesia until the following morning. Patient-controlled analgesia could be discontinued as early as 3:00 AM but no later than 12:00 PM on the first postsurgical day. Patients who developed a level of pain that measured at least 45 mm on a visual analog scale (VAS; ranging, 0–100 mm) and a categorical pain intensity of moderate or severe within 6 h after discontinuation of patient-controlled analgesia were then randomized to receive one intravenous dose of either parecoxib sodium, 20 mg or 40 mg (Pharmacia Corporation, Skokie, IL), ketorolac, 30 mg (Toradol®, Roche Pharmaceuticals, Nutley, NJ), morphine, 4 mg, or placebo. The dose of ketorolac selected was based on previous studies, which compared its analgesic efficacy with parecoxib sodium in the oral surgery model. In these studies, the full therapeutic dose of intravenous ketorolac, 30 mg, was comparable in efficacy with parecoxib sodium, 20 mg and 40 mg.³¹ No previous studies have compared parecoxib sodium with morphine. Therefore, for this study a dose of morphine was chosen that provides a reasonable level of analgesia, without a significant level of euphoric or other nonanalgesic side effects, to ensure that the study was not unblinded with respect to treatment. This study was not designed to calibrate the analgesic activity of parecoxib sodium with morphine. Analgesic activity was assessed during a 24-h treatment period or until rescue analgesia was administered, using the standard measures: time to onset of analgesia, pain relief (PR), pain intensity difference (PID), the time to rescue medication, and the patient's global evaluation of study medication.

Patients were excluded if they were scheduled to undergo surgery likely to produce greater surgical trauma than the hysterectomy or myomectomy alone; had GI bleeding or esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before receipt of study medication; were experiencing significant GI complaints; had received any analgesic (including neuroleptic), antipsychotic, or corticosteroid drugs, other than those required for surgery, within 6 h before surgery (or longer if long-acting or sustained-release formulations of the medication were used); or were hypersensitive to any NSAID, COX-2-specific inhibitors, opiates, or any analgesic agent with cross-reactivity to the study drugs. If a patient had been diagnosed with, treated for, or was in remission from any cancer other than basal cell carcinoma or metastatic uterine carcinoma within 2 yr before screening, they were also excluded.

Eligible patients were randomized to treatment according to a computer-generated schedule in the order in which they were enrolled. All participants were blinded to the identity of the treatments until all study data had been collated in a database. Study medication was administered on the first postoperative surgery day rather than immediately after surgery to reduce the carryover effects of operative anesthesia and analgesic agents. Patients were informed that they could request additional pain medication at any time during the study. No further pain assessments were made after treatment with this rescue medication, which was administered in accordance with the standard practices at each study site. Administration of rescue medication therefore had no effect on the interpretation of the collated pain data.

Assessments

All pain measures used were standard assessments performed by each patient, according to the instructions of trained study personnel present at each designated time-point for the assessment of the patient's pain status. A trained nurse coordinator collected the pain assessment from each patient and recorded the findings on case report forms.

A two-stopwatch technique was used to measure time to onset of analgesia. At the time of study medication administration, study personnel started two stopwatches for each patient. Patients were instructed to stop the first stopwatch when they first experienced perceptible pain relief (*i.e.*, began to feel any pain-relieving effect of the drug) and the second when they first experienced meaningful pain relief (*i.e.*, began to feel their pain relief was meaningful to them).

For the remaining pain assessments, patients measured elicited incisional pain after a standardized provocative log roll movement to either side (same side for each assessment) with the head of the bed lowered to 30°, at baseline and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 h after the administration of study medication.

Patients assessed pain intensity on a categorical scale by completing the following statement: My pain at this time is none, 0; mild, 1; moderate, 2; or severe, 3. Patients also recorded their pain intensity on a VAS by placing a vertical mark on a 100-mm line to indicate the magnitude of their pain (0 = no pain and 100 = most severe pain). VAS and categorical assessments were performed before administration of study medication to obtain a measure of the patient's baseline pain intensity in each treatment group, whereas categorical measurements were performed at all other time-points to evaluate pain intensity for the calculation of pain relief scores. Patients indicated their level of pain relief by completing the statement: My relief from starting pain is none, 0; a little, 1; some, 2; a lot, 3; and complete, 4.

At the end of the 24-h treatment period or just before taking rescue medication, the patient's global evaluation of the study medication was assessed. In response to the question "How would you rate the study medication you received for pain?" patients selected one of the following four options: poor (1), fair (2), good (3), or excellent (4).

Safety and tolerability were assessed by monitoring adverse events. Data of all adverse events occurring throughout the study were obtained by observation and indirect questioning of patients and by assessing changes in physical examination, vital signs, and clinical laboratory values. The clinical laboratory measurements comprised a complete blood count, complete urinalysis (including microscopy), and a biochemistry panel of 16 routine analytes. In addition, prothrombin time, partial thromboplastin time, and platelet counts were also assessed. Physical examinations, clinical laboratory tests, and vital signs were performed at screening (within 14 days of study medication administration), and 24 h post-dose or just before taking rescue medication. In addition, clinical laboratory tests were performed at baseline (before administration of study medication), and vital signs were measured at baseline, and at 1, 2, 4, and 24 h postdose.

Statistics

Sample size was determined based on the PID for each dose of parecoxib sodium *versus* placebo. This study was not powered to compare the relative efficacy of parecoxib sodium with ketorolac or morphine. Based on a previous dental pain study,³¹ a sample size of 40 patients per treatment group was required to detect a difference of at least 0.8 at 45 min, with at least 80% power and type I error at 0.025 (for a two-sided test adjusted for two comparisons), and a SD estimate of 0.88.

Efficacy was assessed using a modified intent-to-treat cohort, predefined as all randomized patients who received study medication, who remained in the study (*i.e.*, did not take rescue medication) at least until the 1-h assessment, and who did not miss two consecutive pain assessments in the first 2 h.

Time to onset of analgesia (defined as the time to perceptible pain relief if the patient experienced perceptible and meaningful pain relief) and time to rescue medication were analyzed using survival analysis methods. Patients who took rescue medication before reaching perceptible pain relief were assigned a time according to the following formula: $24.1 + (0.005/\text{time to rescue})$. Median times to event were calculated for each treatment group using the Kaplan-Meier product limit estimator as adjusted by Miller.³⁴ Survival curves and the overall treatment group comparisons were calculated using the log-rank test. If the overall log-rank test showed significant differences, comparisons were made between the treatment groups using pair-wise log rank tests as in Fisher protected least significant difference method. Confidence intervals (95%) were calculated for the median time to event using the Simon and Lee method.³⁵

The PID was derived by subtracting the pain intensity scores measured at each assessment from the baseline pain intensity score, whereas the summed pain intensity difference (SPID) was defined by summing the time-interval-weighted PID scores from baseline through the 6-, 8-, 10-, 12-, 16-, and 24-h assessments. A greater mean SPID score represents improved pain relief. PID and SPID were analyzed using an analysis of covariance (ANCOVA) model with treatment and center as factors and baseline pain intensity as a covariate. The PR assessments were analyzed using an analysis of variance (ANOVA) model with treatment, center, and treatment by center effects. The patient's global evaluations of study medication were analyzed using ANCOVA with treatment and center as factors and baseline pain intensity as a covariate, in addition to a Cochran-Mantel-Haenszel test stratified by center.

The last observation carried forward approach was used in the analyses of time-specific pain assessments to account for missing data as a result of patients taking rescue medication or withdrawing from the study. Briefly, the last score recorded in any given efficacy assessment before withdrawal was used (carried forward) in the analysis at all subsequent time-points. Thus, only pain assessments before rescue medication were included in the analyses. Isolated missing pain data between observed values were imputed on a patient-by-patient basis by linear interpolation. Fisher protected least significant difference multiple comparison procedure was used for pair-wise comparisons of least squares treatment means. The significance level was predefined as 0.05.

All randomized patients who received at least one dose of study medication were included in the safety analysis. The incidence of adverse events between treatment groups was compared using Fisher exact test.

Table 1. Baseline Characteristics of Patients Randomized to Treatment

	Placebo (n = 42)	Parecoxib Sodium 20 mg IV (n = 39)	Parecoxib Sodium 40 mg IV (n = 38)	Ketorolac 30 mg IV (n = 41)	Morphine 4 mg IV (n = 42)
Age (yr)					
Mean	41.0	43.7	42.0	40.8	40.7
Range	29–63	21–56	29–65	27–52	25–61
Weight (kg)					
Mean	80.3	77.9	77.3	73.2	78.8
Range	50.0–128.6	47.2–152.5	50.0–135.0	45.4–127.3	48.5–127.3
Surgical procedure					
Total abdominal hysterectomy	98%	100%	100%	95%	100%
Myomectomy	2%	0%	0%	5%	0%
Baseline pain intensity	60%	62%	61%	59%	62%
Categorical					
Moderate	60%	62%	61%	59%	62%
Severe	40%	38%	39%	41%	38%
VAS (mean)	66.3%	69.4	67.5	68.3	67.0

IV = intravenous; VAS = visual analog scale.

Results

Patients

Two hundred two patients were enrolled in the study, of whom three patients in the placebo group were withdrawn before completing the 1-h assessment and one patient in the intravenous parecoxib sodium, 20 mg, group was withdrawn because of a protocol violation. Nearly all the patients had undergone total abdominal hysterectomy, and there were no significant differences across the groups in the baseline characteristics of the patients. Between 38% and 41% of patients in each treatment group had severe pain at baseline, with the mean pain intensity as measured on the VAS ranging from 66.3 to 69.4 (table 1).

Efficacy Analyses

Onset of Analgesia. Most patients receiving active treatment (55–93%) experienced analgesia compared with fewer than 40% of patients who received placebo treatment (table 2). In addition, patients receiving active treatments reported a median time to onset of analgesia of between 10 and 23 min compared with more than 24 h (*i.e.*, no meaningful pain relief before rescue medication) for patients receiving placebo treatment. Al-

though the median time to onset of analgesia was significantly faster with intravenous ketorolac, 30 mg, (median 10 min) compared with intravenous parecoxib sodium, 20 mg, (23 min) by the log-rank test, there were no significant differences among the active treatment groups as demonstrated by overlapping confidence intervals.

Pain Intensity Difference. Pain intensity difference scores increased for all treatments over the initial assessment periods, with the maximum PID being reached for all treatments by the 2-h assessment (fig. 1A). The mean PID scores reported by patients in the active treatment groups were significantly greater ($P \leq 0.05$) at most assessments during the 24-h evaluation period compared with those reported by patients treated with placebo. In contrast, the mean PID scores reported by the patients treated with intravenous morphine, 4 mg, were only transiently greater than placebo (during the 0.5- to 1.5-h assessments only; $P \leq 0.05$). The mean PID scores reported by the patients treated with intravenous parecoxib sodium, 20 mg, intravenous parecoxib sodium, 40 mg, and intravenous ketorolac, 30 mg, were similar at most assessments. Further, these agents provided significantly greater reductions in pain intensity than intravenous morphine, 4 mg, over much of the evaluation

Table 2. Onset of Analgesia and Rescue Medication Results

	Time to Onset of Analgesia			Time to Rescue Medication		
	Median*	95% CI	Patients†	Median*	95% CI	Patients†
Placebo	>24:00§ C‡	—	14 (36%)	1:50 B	1:40–3:05	38 (97%)
Parecoxib sodium 20 mg	0:23 B	0:11–>24	25 (66%)	6:10 A	3:54–7:58	35 (92%)
Parecoxib sodium 40 mg	0:14 AB	0:09–0:28	29 (76%)	6:30 A	4:35–9:19	33 (87%)
Ketorolac 30 mg	0:10 A	0:09–0:14	38 (93%)	6:00 A	5:17–7:45	38 (93%)
Morphine 4 mg	0:23 AB	0:06–>24	23 (55%)	2:36 B	2:09–4:14	40 (95%)

* H:min; † Number (%); ‡ Treatments with the same letter are not statistically significant from each other by the log rank test; § The median time could not be estimated since less than 50% of the patients in the placebo group experienced an onset of analgesia by the end of the 24-h study period. The time to onset was, therefore, considered to be >24 h.

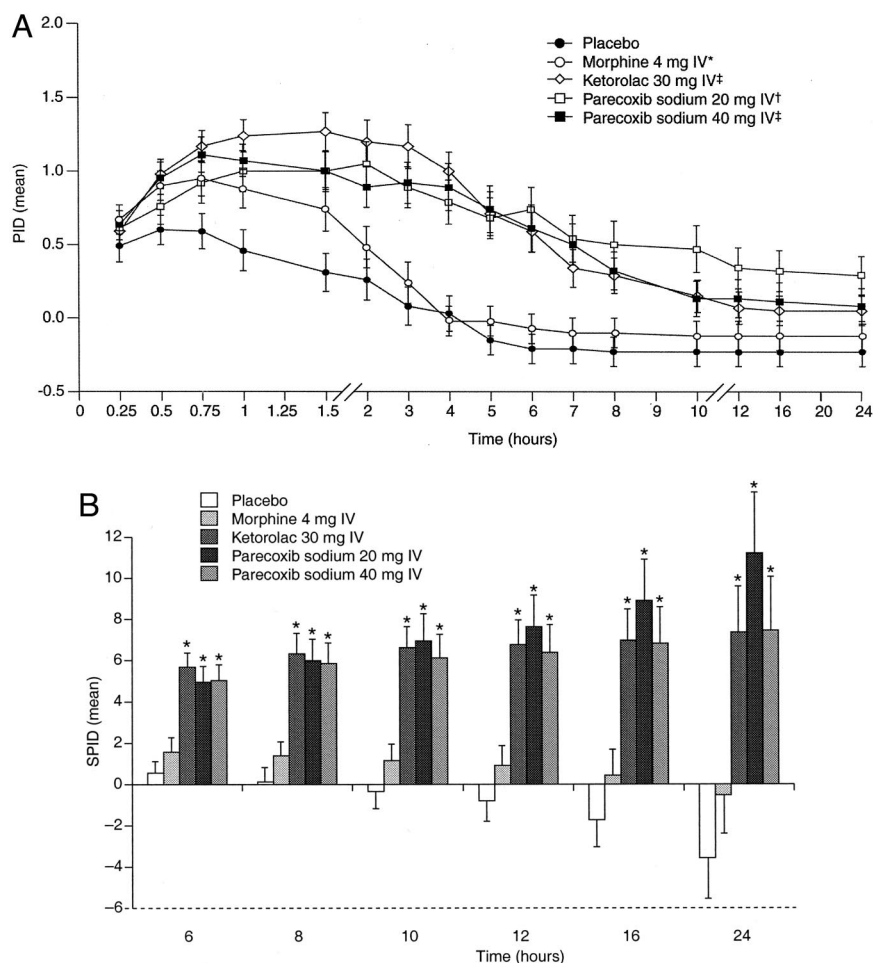


Fig. 1. (A) Pain intensity difference mean scores over 24 h. $P \leq 0.05$ versus placebo from *0.5–1.5 h, †0.5–24 h, ‡0.75–24 h. (B) Summed pain intensity difference mean scores over 24 h. * $P \leq 0.05$ versus placebo or morphine at all time points. Bars above and below each mean value represent the SEM.

period, consistent with the transient effect of this dose of morphine.

Summed Pain Intensity Difference. As shown in figure 1B, the mean time-interval-weighted SPID scores increased with all of the treatments except intravenous morphine, 4 mg, and placebo during the 24-h assessment period. The mean scores for patients treated with intravenous morphine, 4 mg, decreased during the assessment period, becoming negative by the 24-h assessment. The mean scores for patients treated with placebo were also negative by the 10-h assessment. Patients treated with either dose of intravenous parecoxib sodium or intravenous ketorolac, 30 mg, had similar SPID scores, which were significantly higher ($P \leq 0.05$) than those recorded for patients treated with intravenous morphine, 4 mg, or placebo at all times at which SPID was calculated. Decreasing SPID scores over time for placebo and morphine are consistent with a worsening of pain compared with baseline, as would be expected for an ineffective or minimally effective analgesic treatment.

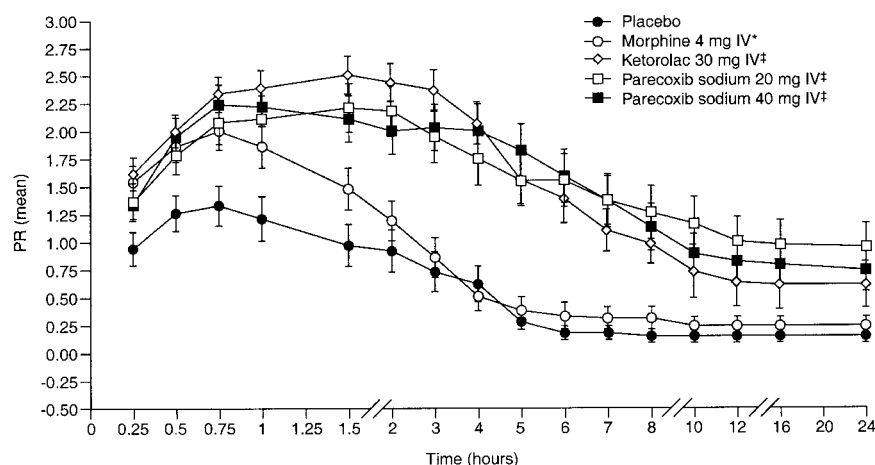
Pain Relief. Figure 2 shows that patients experienced greater relief from pain with intravenous parecoxib sodium (both doses) and intravenous ketorolac, 30 mg, than with placebo, with maximum relief being reached by the 1.5-h assessment. The mean PR scores were sig-

nificantly greater ($P \leq 0.05$) for patients treated with intravenous parecoxib sodium, 20 mg, intravenous parecoxib sodium, 40 mg, and intravenous ketorolac, 30 mg, at all assessment times compared with those treated with placebo. Whereas the mean PR scores reported by patients treated with morphine from the 2-h assessment onward decreased below their mean score at the initial assessment, the effects of intravenous parecoxib sodium and intravenous ketorolac, 30 mg, were more sustained. The mean PR scores for patients treated with each dose of intravenous parecoxib sodium or intravenous ketorolac, 30 mg, were similar at all the assessments.

Time to Rescue Medication. The proportion of patients who took rescue medication was similar (87–97%) for all groups (table 2). Rescue medication mostly consisted of one or more doses of acetaminophen or a combination of hydrocodone and acetaminophen; the quantity of rescue medication received and its effect on subsequent pain scores were not evaluated.

The median time to rescue medication for patients who received intravenous parecoxib sodium or intravenous ketorolac, 30 mg, ranged from 6 h to 6.5 h; based on the nonoverlapping 95% confidence intervals, these times were significantly longer than the median time to rescue medication for placebo (1 h 50 min). Treatment

Fig. 2. Mean pain relief scores. * $P \leq 0.05$ versus placebo from 0.25–1 h or ‡at all other time points. Bars above and below each mean value represent the SEM.



with intravenous parecoxib sodium, 40 mg, and intravenous ketorolac, 30 mg, resulted in significantly longer median time to rescue medication than intravenous morphine, 4 mg, (2 h 36 min).

Figure 3 shows the distributions of the time to rescue medication for all the study groups. All patients treated with placebo, intravenous morphine, 4 mg, or intravenous ketorolac, 30 mg, had taken rescue medication by the 16-h assessment. The distribution of times to rescue medication suggested a generally longer duration of analgesia for parecoxib sodium, 40 mg, compared with ketorolac, although the variability in the data resulted in comparable median rescue times.

Patients' Global Evaluation of Study Medication

At the end of the study, few patients receiving placebo rated their medication as "good" or "excellent," whereas the majority of patients receiving active treatment rated their medication as "good" or "excellent" (fig. 4). Patients receiving either dose of intravenous parecoxib sodium or intravenous ketorolac, 30 mg, had comparable mean patient's global evaluation scores that were significantly greater ($P \leq 0.005$) than patients treated

with intravenous morphine, 4 mg, or placebo. All active treatments received significantly ($P \leq 0.05$) better patient global evaluations than placebo treatment.

Safety Analysis

The most common adverse events recorded in the study are listed in table 3. The majority of adverse events were classified as mild or moderate in nature, with only two patients, both in the intravenous morphine, 4 mg, group, having adverse events classified as serious (pulmonary emboli, persistent nausea and vomiting). However, these serious adverse events were not considered to be treatment related by the investigator. Twenty patients withdrew from the study because of adverse events, four or five from each of the active treatment groups and two from the placebo group. Headache (all treatments) and fever (ketorolac) were the most common reasons for withdrawal from the study.

Adverse events were reported for 74% of patients treated with placebo, 87% of patients treated with intravenous parecoxib sodium, 20 mg, 84% of patients treated with intravenous parecoxib sodium, 40 mg, 93% of patients treated with intravenous ketorolac, 30 mg, and 88% of patients treated with intravenous morphine,

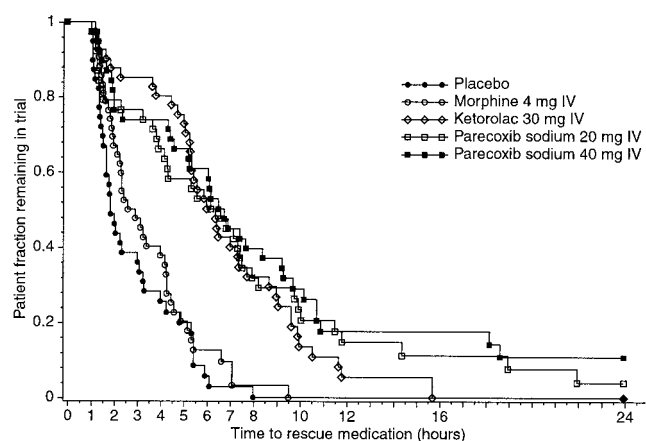


Fig. 3. Time to rescue medication (Kaplan-Meier product limit estimates).

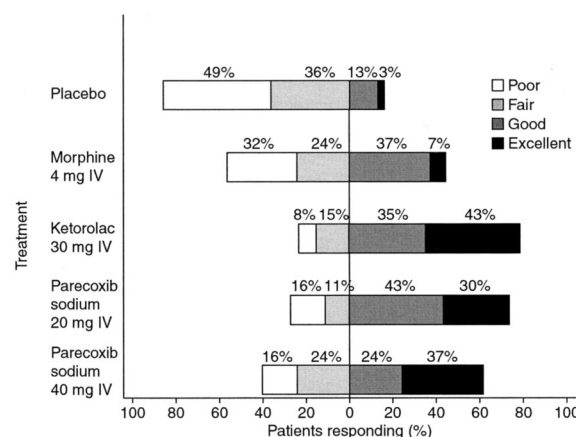


Fig. 4. Patients' global evaluation of study medication.

Table 3. Adverse Events Occurring in at least 10% of Patients

	Placebo (n = 42)	Parecoxib Sodium 20 mg IV (n = 39)	Parecoxib Sodium 40 mg IV (n = 38)	Ketorolac 30 mg IV (n = 41)	Morphine 4 mg IV (n = 42)
Any event	31 (74%)	34 (87%)	32 (84%)	38 (93%)*	37 (88%)
Withdrawals	2 (5%)	5 (13%)	4 (11%)	5 (12%)	4 (10%)
Back pain	2 (5%)	3 (8%)	1 (3%)	1 (2%)	5 (12%)
Fever	10 (24%)	0*†	2 (5%)*	6 (15%)	5 (12%)
Nausea	16 (38%)	13 (33%)	12 (32%)	17 (42%)	13 (31%)
Vomiting	5 (12%)	6 (15%)	9 (24%)	11 (27%)	10 (24%)
Abdominal pain	11 (26%)	9 (23%)	9 (24%)	12 (29%)	8 (19%)
Abdominal fullness	13 (31%)	6 (15%)	4 (11%)*	5 (12%)	4 (10%)*
Hypoactive bowel sounds	4 (10%)	4 (10%)	1 (3%)	2 (5%)	3 (7%)
Dizziness	6 (14%)	4 (10%)	5 (13%)	7 (17%)	5 (12%)
Headache	9 (21%)	8 (21%)	10 (26%)	8 (20%)	10 (24%)
Tachycardia	0	2 (5%)	0‡	2 (5%)	6 (14%)*
Somnolence	4 (10%)	1 (3%)	0‡	3 (7%)	7 (17%)
Abnormal breath sounds	8 (19%)	7 (18%)	5 (13%)	5 (12%)	5 (12%)
Pruritus	3 (7%)	7 (18%)	2 (5%)	3 (7%)	5 (12%)

Patients may have reported more than one adverse event.

* $P < 0.05$ versus placebo; † $P < 0.05$ versus ketorolac; ‡ $P < 0.05$ versus morphine.

IV = intravenous.

4 mg. The average number of adverse events for patients experiencing events was two per patient in each treatment group. The majority of adverse events were related to the GI system, and the incidence of these was similar among the active treatment and placebo groups. Significantly more ($P \leq 0.05$) patients treated with placebo reported fever (24%) compared with patients treated with either the intravenous parecoxib sodium, 20 mg, (0%) or intravenous parecoxib sodium, 40 mg (5%). In addition, significantly fewer patients treated with intravenous parecoxib sodium, 20 mg, reported fever compared with patients receiving intravenous ketorolac, 30 mg (15%, $P \leq 0.05$). The incidence of somnolence and tachycardia among patients receiving intravenous morphine, 4 mg, was significantly greater than in patients receiving parecoxib sodium, 40 mg ($P < 0.05$). There was no evidence of a dose-related increase in the incidence of adverse events with parecoxib sodium, 20 or 40 mg, doses. There were no clinically significant changes from baseline in vital signs, physical examination results, or clinical laboratory parameters, including prothrombin time, partial thromboplastin time, and platelet counts in patients receiving placebo or any active treatment. There were also no consistent, clinically meaningful trends in clinical laboratory test results within treatment groups or with increasing dosage of parecoxib sodium.

Discussion

This study evaluated the analgesic efficacy and safety of single intravenous doses of a new, injectable COX-2-specific inhibitor, parecoxib sodium, in patients with acute postoperative pain after gynecologic laparotomy surgery. The results of this study confirmed the hypoth-

esis that an injectable COX-2-specific inhibitor would be at least as effective and well tolerated as a COX-nonspecific conventional NSAID, ketorolac. In terms of the speed of onset of analgesia and of the general magnitude of analgesia (degree of PR and pain intensity), intravenous parecoxib sodium, 20 mg and 40 mg, were comparable with intravenous ketorolac, 30 mg, for managing acute postlaparotomy pain. The duration of pain relief after single-dose therapy with parecoxib sodium and ketorolac was similar, although based on the ranges of time to rescue, there is a pattern of longer analgesic activity with 40 mg of parecoxib sodium relative to ketorolac. This trend is not unexpected as it is consistent with the differing pharmacokinetic profiles of the two agents.²⁸

The findings of this study provide data regarding the question of the relative analgesic potency of COX-2-specific versus COX-nonspecific NSAIDs. The study results support the conclusion that the inhibition of COX-2 is responsible for the observed therapeutic effects of NSAIDs. The comparability of the maximum therapeutic dose of intravenous ketorolac, 30 mg, to intravenous parecoxib sodium, 40 mg, suggests that the effects of COX-1 inhibition are not associated with analgesic activity, a conclusion consistent with the prevailing hypothesis that COX-2-specific agents can have the same efficacy as COX-nonspecific NSAIDs without the added burden of symptoms and adverse effects resulting from COX-1 inhibition. A related question is whether COX-2-specific agents are potentially more efficacious than mixed COX inhibitors. However, the similar analgesic effects of the two doses of intravenous parecoxib sodium evaluated in this study suggest that doses exceeding 40 mg may not provide any further analgesic benefit in this model of postsurgical pain.

The analgesic activity of parecoxib sodium in comparison with low dose (4 mg, intravenous) morphine, although not a primary endpoint of the study, demonstrated a pattern of greater analgesic effect with parecoxib sodium. This finding is not unexpected because the analgesic effect of this dose of morphine is understood to be short-lived, and patients would customarily receive additional morphine as necessary to titrate to adequate pain relief. Nonetheless, the data are helpful to some degree in understanding the potency of parecoxib sodium in managing postoperative pain. However, additional studies against higher doses of morphine would be helpful in this regard. For comparison, intramuscular ketorolac, 30 mg, is generally considered comparable with 6–12 mg of intramuscular morphine.³⁶ In so far as parecoxib sodium, 40 mg, and ketorolac, 30 mg, were comparable, a reasonable estimate of the potency of parecoxib sodium is that it would be within a similar range of opiate activity, that is, between 6–12 mg of morphine. However, it should be noted that morphine is less effective in the management of pain on movement,³⁷ which was the method of pain assessment used in this study, and this may explain the comparatively poor efficacy of morphine, 4 mg, relative to ketorolac, 30 mg, and parecoxib sodium, 20 mg and 40 mg.

Parecoxib sodium was well tolerated in this trial. Adverse events were frequent regardless of treatment, consistent with the common occurrence of symptoms during the immediate postoperative period. Importantly, no evidence of treatment-related serious adverse events, such as wound bleeding, renal dysfunction, or upper GI bleeding, was seen with parecoxib sodium. The incidence of adverse events was similar among active treatment and placebo groups. Of note, however, is the finding that parecoxib sodium treatment resulted in a significant reduction in fever compared with placebo, which is consistent with its antiinflammatory action. A reduction in opioid-type side effects with parecoxib sodium or ketorolac relative to morphine would not necessarily be expected with single-dose treatment, particularly because patients were permitted patient-controlled analgesia with morphine or meperidine hydrochloride for several hours before receiving study medication.

In conclusion, the results of this study indicate that the novel COX-2-specific analgesic antiinflammatory agent parecoxib sodium is an effective analgesic in patients after laparotomy surgery. As evaluated in this single-dose analgesia model, parecoxib sodium, 20 mg and 40 mg, are at least as effective as intravenous ketorolac, 30 mg, and appear to be superior to intravenous morphine, 4 mg. These findings suggest that parecoxib sodium will be an effective and well-tolerated injectable analgesic for the management of postoperative pain after gynecologic surgery. On the basis of its COX-2 selective mechanism of action, it has been predicted that parecoxib sodium

may offer safety advantages over COX-nonselective agents for use in the perioperative period.²⁹ However, additional studies involving larger numbers of patients will be needed to clearly validate this hypothesis, especially with regard to platelet, renal, and GI effects.

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Appendix

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