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## Assessment of Ketorolac as an Adjuvant to Fentanyl Patient-controlled Epidural Analgesia after Radical Retropubic Prostatectomy

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**Background:** Opioids, although effective postoperative analgesics, are associated with undesirable side effects. In an attempt to determine whether adjuvant, nonopioid medication would permit a reduction of the amount of fentanyl required for postoperative analgesia, the efficacy of ketorolac, an injectable nonsteroidal antiinflammatory drug, was studied as an adjuvant to fentanyl patient-controlled epidural analgesia (PCEA) for postoperative pain management following radical retropubic prostatectomy.

**Methods:** Forty patients were randomized into two groups to receive fentanyl PCEA and either ketorolac 30 mg intramuscularly every 6 h after an initial dose of 60 mg ( $n = 20$ ) or placebo ( $n = 20$ ) for 72 h. Visual analogue scale pain scores (0-100 mm; 0 mm = no pain; 100 mm = worst pain), sedation, fentanyl usage, gastrointestinal function, complications, blood loss, and temperature were assessed four times each day.

**Results:** Visual analogue scale (VAS) pain scores at rest were lower in the ketorolac group during the first 4 h ( $P < 0.01$ ), but were similar thereafter. Global VAS pain scores with activity were lower in the ketorolac group on postoperative day 1 ( $23 \pm 4$  vs.  $39 \pm 6$ ;  $P < 0.05$ ) and postoperative day 2 ( $17 \pm 3$  vs.  $29 \pm 4$ ;  $P < 0.05$ ). Bladder spasm pain occurred less frequently in the ketorolac group (1 vs. 9 patients;  $P < 0.05$ ).

Fentanyl usage was less in the ketorolac group throughout the study ( $33 \pm 3$  vs.  $50 \pm 6$   $\mu\text{g}/\text{h}$ , 0-24 h;  $20 \pm 2$  vs.  $36 \pm 6$   $\mu\text{g}/\text{h}$ , 24-48 h;  $12 \pm 2$  vs.  $24 \pm 6$   $\mu\text{g}/\text{h}$ , 48-72 h;  $P < 0.05$ ). Sedation scores and side effects were similar, except on postoperative day 3 when nausea was less frequent in the ketorolac group (0 vs. 6 patients;  $P < 0.05$ ). Recovery of gastrointestinal function occurred sooner in the ketorolac group as determined by first bowel sounds ( $26 \pm 3$  vs.  $38 \pm 4$  h;  $P < 0.05$ ), first clear liquids ( $51 \pm 2$  vs.  $65 \pm 3$  h;  $P < 0.01$ ), and first regular meal ( $95 \pm 4$  vs.  $110 \pm 4$  h;  $P < 0.05$ ). There was no significant difference in blood loss, transfusion requirement, hematocrit, platelet count, or temperature. There was high overall satisfaction in both groups, but fewer patients in the ketorolac group rated pain with walking as usually or always painful (1 vs. 9 patients;  $P < 0.05$ ).

**Conclusions:** Ketorolac is a beneficial adjuvant to fentanyl PCEA for postoperative pain management after radical retropubic prostatectomy. (Key words: Analgesics: fentanyl; ketorolac. Anesthetic techniques: epidural. Pain, postoperative: urologic surgery. Patient-controlled epidural analgesia.)

KETOROLAC is a nonsteroidal agent with potent analgesic and moderate antiinflammatory activity. It is the only nonsteroidal antiinflammatory drug (NSAID) commercially available in injectable form. In some settings, ketorolac has been useful as an alternative to opioid agents for the management of postsurgical pain. Clinical studies indicate that single-dose analgesic efficacy is comparable to that of morphine and meperidine for moderate-to-severe postoperative pain.<sup>1-3</sup> Some evidence indicates fewer adverse side effects than with opioid analgesics.<sup>4,5</sup>

Two recent studies examined the efficacy of ketorolac in combination with intravenous patient-controlled analgesia (IV-PCA) in postoperative gynecological surgery patients.<sup>6,7</sup> In both studies, ketorolac significantly decreased the postoperative morphine requirements. Parker *et al.* found that patients receiving ketorolac as an adjuvant to either morphine or meperidine IV-PCA resumed bowel function sooner and were discharged from the hospital significantly earlier.<sup>6</sup>

Epidural opioids administered either as a continuous infusion or as patient-controlled epidural analgesia (PCEA) are frequently used to manage postoperative

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pain. Although this therapy provides excellent pain relief and a high degree of patient satisfaction, it may be associated with a substantial incidence of dose-dependent side effects, including sedation, nausea and vomiting, pruritus, and delayed return of bowel function. We designed a randomized, double-blind, placebo-controlled study to examine the effects and interactions of ketorolac with fentanyl PCEA. We studied dose requirements, effectiveness of analgesia, incidence of side effects, recovery of gastrointestinal function, and patient acceptance/satisfaction after radical retropubic prostatectomy.

### Materials and Methods

With approval of the Johns Hopkins Joint Committee on Clinical Investigation and informed consent, we studied 40 ASA physical status 1, 2, and 3 patients scheduled for elective radical retropubic prostatectomy surgery with epidural anesthesia. Premedication with oral diazepam or intramuscular (IM) midazolam was administered at the discretion of the responsible anesthesiologist. An epidural catheter was inserted at either the L<sub>2-3</sub>, L<sub>3-4</sub>, or L<sub>4-5</sub> interspace. Anesthesia was established with 2% lidocaine with epinephrine, 1:200,000. Subsequent doses of epidural lidocaine were given as clinically indicated to maintain a T<sub>4</sub> level of sensory blockade. Intravenous midazolam and/or fentanyl were used for sedation or analgesia during the surgical procedure, as necessary. No fentanyl was given through the epidural catheter.

After the first complaint of pain in the postanesthesia care unit (PACU), both pain and sedation were assessed using standard 100-mm visual analogue scales (VAS), and one of the two randomly assigned double-blind postoperative analgesia regimens was begun. The ketorolac group (n = 20) received fentanyl PCEA and ketorolac, while the control group (n = 20) received fentanyl PCEA and placebo (saline). Throughout the study, all epidural fentanyl was administered as 20 µg in 1 ml of saline. Initiation of postoperative analgesia in the PACU for both groups consisted of a bolus of 50 µg of fentanyl through the epidural catheter followed by PCEA with a basal rate of 30 µg/h, a demand dose of 20 µg of fentanyl, and a 10-min lockout period. At the same time, patients in the ketorolac group received 60 mg of ketorolac IM and control patients received 2 ml of saline IM. Thereafter, ketorolac patients received 30 mg of ketorolac IM every 6 h and control patients received 1 ml of saline IM every 6 h for 72 h. The study continued until 7 PM on postoperative day 3. If anal-

gesia was inadequate or if the patient had used more than three demand doses over any 1-h interval, the demand dose of fentanyl was increased by 20 µg and the basal rate was increased by 20 µg/h. No reductions in the PCEA regimen were made on the day or the night immediately following surgery unless the patient experienced moderate or greater sedation, respiratory rate decreased to <12, or other adverse side effects were observed.

Visual analog scale pain scores were obtained after the first complaint of pain in the PACU and at 15, 30, and 60 min after initiating the analgesic regimen. Subsequent VAS pain scores were obtained at 2, 4, and 6 h.

On postoperative day 1, 2, and 3, patients were evaluated at 7 AM, 11 AM, 3 PM, and 7 PM. Evaluations included VAS pain scores and sedation scores using a similar 100-mm visual analogue sedation scale. Other observations included the presence or absence and severity of pruritus, the presence or absence of nausea and/or vomiting, and the presence or absence of bladder spasm pain. During the final evaluation of the day, global sedation, pain at rest, dynamic pain, and patient satisfaction scores were obtained.

Beginning with the first evaluation on postoperative day 1 and at each subsequent evaluation, epidural dose adjustments were made according to the following scheme. First, if the patient complained of inadequate analgesia or had required more than three demand doses in a 1-h interval, both the basal rate and the demand dose were increased by 20 µg. The maximum PCEA regimen permitted was a basal rate of 50 µg/h and a demand dose of 60 µg. Second, if patients had not previously had dose increases and their demand doses had been < 1/h over the previous 4 h, the basal rate was reduced by 20 µg/h to a minimum of 10 µg/h. If demand dosing continued at <1/h while the basal rate was 10 µg/h, the basal infusion was discontinued. Third, if patients had had a previous increase in their PCEA dose, but subsequently reduced doses to <1/h, the basal rate was decreased by 20 µg/h. If self-dosing continued at <1/h, the demand dose was decreased by 20 µg. Fourth, for periods during which patients continued to use <1/h, the basal rate and demand dose continued to be alternately decreased by 20 µg until a minimum of 10 µg/h basal rate and a minimum 20-µg demand dose were administered. If demand doses continued at <1/h, the basal infusion was discontinued.

Throughout the study period, side effects were treated similarly for both groups. Pruritus was treated with an infusion of naloxone 20 µg/h (which was discontinued

after 24 h if the pruritus resolved). Nausea and/or vomiting were treated with metoclopramide 10 mg IV every 4 h as needed.

The study period terminated at 7 PM on postoperative day 3. Each patient then completed a final questionnaire concerning his perception of the postoperative analgesic care. Patients' charts were reviewed for the following information: patient age, height, weight, ASA physical status, duration of surgery, total dose of epidural lidocaine, total dose of intravenous midazolam and fentanyl, length of time in PACU, and duration of postoperative hospital stay, time from the end of surgery until the first time the patient was out of bed, time until the first time bowel sounds were recorded, time until the first flatus was passed, time until the first bowel movement, time until first clear liquid intake, and time until the first regular meal was tolerated. Other data compiled included estimated intraoperative blood loss; number of units of transfused blood required; and hematocrit preoperatively, in PACU, and on postoperative days 1 and 3. Platelet count was recorded preoperatively and on postoperative days 1 and 3. Surgical drain output was recorded on postoperative days 0, 1, and 2. Maximum temperature was noted on each postoperative day. All data regarding dosage changes and cumulative doses of fentanyl were also recorded.

Statistical analysis included analysis of variance and unpaired Student's *t* tests for continuous data and the VAS pain data. Chi-squared analysis, Mann-Whitney U tests, and Fisher-Yates exact tests were used for non-parametric and demographic data. A *P* value of a type 1 error being less than 0.05 was considered significant. All data are reported as mean  $\pm$  SEM unless otherwise noted.

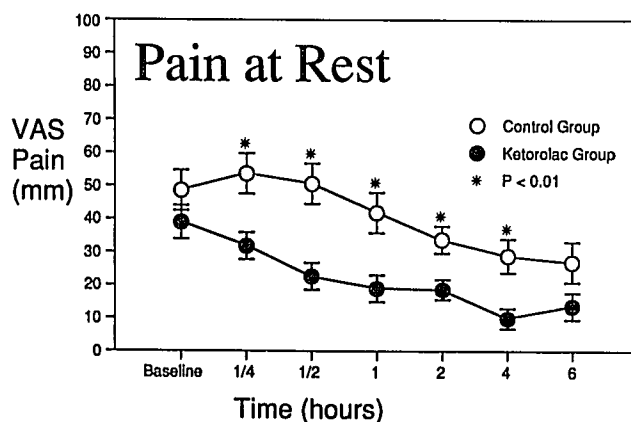
## Results

All 20 patients in each group had successful epidural anesthesia for their surgery. Postoperatively, there were

**Table 1. Demographic Data**

ASA Physical Status	Control Group (n = 20)	Ketorolac Group (n = 20)
1	3	3
2	17	12
3	0	5
4 and 5	0	0
Age (yr)	58 $\pm$ 2	62 $\pm$ 1*
Height (cm)	177 $\pm$ 2	183 $\pm$ 2*
Weight (kg)	82 $\pm$ 2	89 $\pm$ 2*

\* *P* < 0.05 vs. control group.



**Fig. 1. Visual analogue pain scores (in mm) at rest during the 6 h after initiation of the analgesic protocols for both the control group and the ketorolac group. Bars represent SEM; \**P* < 0.05.**

no epidural catheter-related complications or unintended discontinuations in either group. Three patients (one in the control group and two in the ketorolac group) terminated the study on postoperative day 3 before actual completion of the study because they preferred to receive oral analgesics. None of these three patients were experiencing any complications or side effects.

Demographic data are presented in table 1. There were no differences in ASA physical status between the two groups. Although age, height, and weight were all greater in the ketorolac group, these differences were not clinically significant. There was no difference in the intraoperative IV administration of midazolam (6.5  $\pm$  0.5 mg in the control group vs. 6.5  $\pm$  1.0 mg in the ketorolac group), or in the intraoperative IV administration of fentanyl (200  $\pm$  25  $\mu$ g in the control group vs. 150  $\pm$  25  $\mu$ g in the ketorolac group).

Figure 1 shows the VAS pain scores at rest for each group during the first 6 h following initiation of analgesic therapy in the PACU. Pain scores were lower in the ketorolac group at 15 and 30 min and at 1, 2, and 4 h (*P* < 0.01). There was no difference in VAS pain scores at rest after the first 4 h. Figure 2 shows daily global VAS pain scores at rest. There were no significant differences between the two groups. Figure 2 also shows daily global VAS pain scores with activity (getting out of bed and ambulating). These scores were significantly lower in the ketorolac group on postoperative days 1 and 2.

The number of patients rating bladder spasm pain as moderate or severe during the study was less in the

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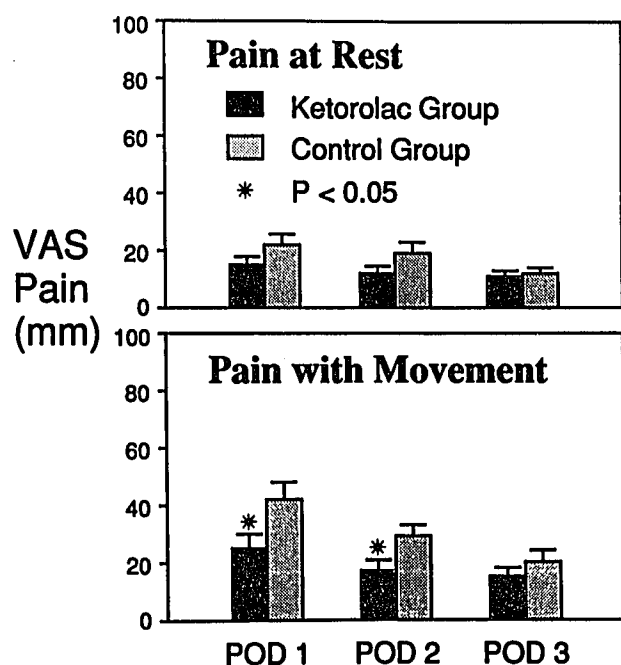


Fig. 2. Daily global visual analogue pain scores (in mm) for control group and ketorolac group during the first 3 postoperative days. Upper panel shows pain scores while resting in bed. Lower panel shows scores during activity such as getting out of bed and walking. Bars represent SEM; \* $P < 0.05$ .

ketorolac group, one patient *versus* nine patients in the control group ( $P < 0.05$ ).

Daily usage of fentanyl and hourly rate of usage were lower in the ketorolac group during all 3 days of the study (table 2).

Sedation scores were higher in the control group during the baseline measurement period ( $48 \pm 5$  vs.  $31 \pm 5$  mm;  $P < 0.05$ ). However, there were no significant differences in sedation scores between the two groups at 15 min after initiating postoperative analgesia and throughout the remainder of the study period.

Only minor differences in side effects were observed between the two groups. There was no significant difference in the incidence of nausea between groups on the day of surgery and on postoperative days 1 and 2.

Table 2. Hourly Fentanyl Usage ( $\mu\text{g}$ )

Time Period (h)	Control Group (n = 20)	Ketorolac Group (n = 20)
0-24	$50 \pm 6$	$33 \pm 3^*$
24-48	$36 \pm 6$	$20 \pm 2^*$
48-72	$24 \pm 6$	$12 \pm 2^*$

\*  $P < 0.05$  vs. control group.

However, there were fewer patients with nausea on postoperative day 3 in the ketorolac group (0 vs. 6 in the control group;  $P < 0.05$ ). There were no differences between groups in the incidence of vomiting throughout the study. Likewise, the incidence of pruritus was similar for both groups throughout the study. Only mild pruritus occurred and no patient required naloxone treatment.

Gastrointestinal recovery times are summarized in figure 3. Patients in the ketorolac group had significantly earlier recovery of bowel sounds, earlier intake of clear liquids, and earlier intake of their first regular meal. There was no difference between the two groups in the time until first passage of flatus.

There were no differences between the groups with respect to intraoperative estimated blood loss, units of blood transfused, or hematocrit throughout the study period. On postoperative day 1, surgical drain output was significantly greater in the ketorolac group ( $156 \pm 29$  vs.  $77 \pm 11$  ml;  $P < 0.05$ ), but was not thereafter. The platelet count was lower in the ketorolac group on postoperative day 1 ( $189,000 \pm 10,000$  vs.  $226,000 \pm 11,000$   $\text{mm}^{-3}$ ;  $P < 0.05$ ), but not on postoperative day 3. No patient in either group had a platelet count below  $150,000$   $\text{mm}^{-3}$ . No patient in either group experienced any clinically significant bleeding complications.

The maximum recorded temperature in the ketorolac group on postoperative day 2 was lower than in the control group ( $37.7 \pm 0.1^\circ\text{C}$  vs.  $38.0 \pm 0.1^\circ\text{C}$ ;  $P < 0.05$ ). At all other times, temperatures were similar. No patient in either group developed or required treatment for any infection.

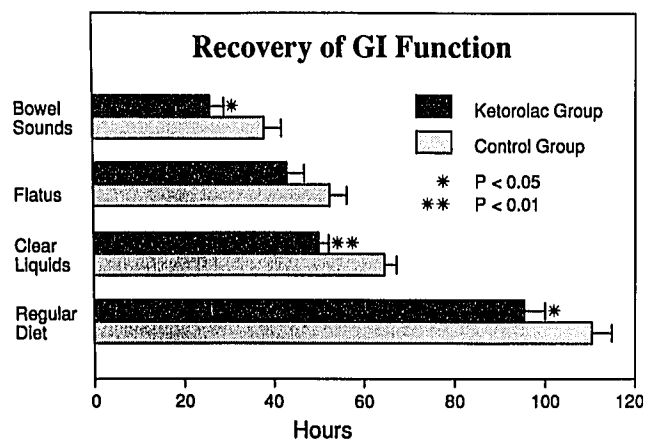


Fig. 3. Times (in hours) to return of several measures of gastrointestinal function for control group and ketorolac group. Bars represent SEM; \* $P < 0.05$ ; \*\* $P < 0.01$ .

Responses to the summary questionnaire administered at the end of the study revealed that overall VAS satisfaction scores were similar,  $92 \pm 2$  mm for the ketorolac group and  $89 \pm 2$  mm for the control group. All patients in both groups indicated that, if offered a choice, they would choose the same postoperative analgesic regimen for future surgeries. Similarly, all patients who had received intramuscular or subcutaneous opioids after a previous abdominal surgery (six in the control group and seven in the ketorolac group) strongly preferred their current regimen. The final questionnaire did, however, reveal clinically significant overall differences between groups with regard to dynamic pain relief. Nineteen of the 20 patients in the ketorolac group recalled pain during walking as "never" or "only occasionally" painful. One patient in the ketorolac group rated walking pain as "usually painful." In the control group, only 11 of the 20 patients rated pain during walking as "painless" or "occasionally painful," while the other nine patients rated the pain as "usually or always painful" ( $P < 0.05$  compared with the ketorolac group).

## Discussion

In this study, we examined the effects of ketorolac in combination with epidural fentanyl in providing analgesia for patients undergoing major lower abdominal surgery. Ketorolac is a nonsteroidal antiinflammatory drug that inhibits the synthesis of prostaglandins and exhibits its analgesic effects at peripheral nerve terminals.<sup>8</sup> Epidural fentanyl probably provides its analgesic effect through both a direct action at spinal cord opioid receptors and centrally through systemic uptake.<sup>9,10</sup> Our study was designed to discover whether the combination of these two different analgesic drugs, acting at separate nociceptive processing sites with different antinociceptive characteristics, would provide superior analgesia while resulting in fewer side effects.

The most significant finding of our study was that the patients receiving ketorolac had similar pain scores at rest, but significantly lower pain scores related to getting out of bed and walking. Although most studies have shown a positive effect of NSAIDs on postoperative pain and reduced requirements for parenteral and/or oral opioids after abdominal surgery,<sup>3,6,7,11-13</sup> Mogensen *et al.*<sup>14</sup> were unable to show enhanced analgesia by adding rectal piroxicam (another NSAID) to a low-dose continuous epidural infusion of bupivacaine plus morphine after major upper abdominal surgery. Their re-

sults may be explained by the assumption that the epidural combination of an opioid and local anesthetic was sufficiently effective that pain after major laparotomy could not be further reduced by adding a NSAID. However, our study indicates that the addition of parenteral ketorolac to an epidural opioid regimen (without local anesthetic) may offer an efficacious alternative to the addition of epidural local anesthetics, while avoiding the risks of hypotension and neural blockade that may result from the use of an epidural local anesthetic.

A second important finding of our study was that the patients in the ketorolac group had a more rapid return of bowel function as evidenced by earlier return of bowel sounds, earlier ability to take clear liquids, and earlier progression to a regular diet based on similar clinical indications. Presumably, this was related to the 40% reduction in opioid usage and reduced adverse systemic opioid effects on bowel motility. A third finding of our study was a lower incidence of bladder spasm pain in the ketorolac group. This finding is consistent with previous studies that concluded that prostaglandins play a role in the mechanism of bladder spasm.<sup>15-17</sup> Although there was a similarly low incidence of vomiting in both the ketorolac and control groups, there was a significantly reduced incidence of nausea on postoperative day 3 in the ketorolac group as compared with the control group.

These results suggest important clinical improvements in outcome, as well as the potential for reduced hospital costs. Despite similar pain scores at rest, the ketorolac group had significantly lower dynamic pain scores, which may translate into more frequent and active ambulation and, possibly, a lower incidence of thrombophlebitis and its complications, as well as pneumonia. In our radical retroperitoneal patients, discharge from the hospital is primarily determined by 24 h of satisfactory outcome after removal of the surgical drains on postoperative day 7. Therefore, earlier return of bowel function did not affect length of hospital stay in our study. However, in a group of patients for whom return of bowel function and the ability to take oral nutrition are the limiting factors, hospital stay should have been significantly shorter in the ketorolac group, as was demonstrated by Parker *et al.*<sup>6</sup> with the use of ketorolac as an adjuvant to IV-PCA after abdominal hysterectomy.

Ketorolac does have side effects that may be deleterious. Ketorolac shares with other NSAIDs an inhibitory effect on platelet aggregation. In our patients, this side

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effect may have accounted for an increased surgical drain output on postoperative day 1. Despite the statistical difference in surgical drain output, none of the patients in either group required blood transfusion after postoperative day 1; throughout the study, both groups had similar hematocrit profiles. We interpret this similarity between the ketorolac and control groups to indicate that the effect, if any, of ketorolac on postoperative bleeding was of no clinical significance. Although multiple-dose, *in vivo* studies in humans have shown that ketorolac inhibits platelet aggregation<sup>18,19</sup> while prolonging bleeding time to a degree similar to that observed with other NSAIDs,<sup>19,20</sup> ketorolac appears not to affect prothrombin time or partial thromboplastin time,<sup>21</sup> and bleeding complications have not been observed in previous clinical trials.<sup>5,22,23</sup> A second side effect of ketorolac that is of concern in the postoperative period is its antipyretic effect. In our study, a significant difference in maximum temperature was observed only on postoperative day 2. However, because it did not appear that ketorolac masked any significant fevers, this antipyretic effect was also of no clinical importance. Similarly, previous clinical trials have not shown a reduction in the incidence of fevers or detection of postoperative infectious complications in patients receiving ketorolac in comparison to parenteral opioids.<sup>5,22,23</sup> Nonetheless, the antipyretic effect of ketorolac may still be of concern.

Despite a 40% reduction in fentanyl usage, the level of sedation and the incidence of pruritus were not reduced in the ketorolac group. Because ketorolac has some sedative effect,<sup>1</sup> it is not surprising that the sedation scores of the ketorolac and control groups were similar. It is also not surprising that the incidence of pruritus was similar in the ketorolac and control groups because, in the dose ranges used in this study, pruritus related to epidural fentanyl is probably not dose-related.<sup>24</sup>

Overall patient satisfaction was similarly high in both groups, probably because both groups received PCEA with fentanyl, which offers the psychological and pharmacokinetic advantages of the PCA mode of administration. Also, treatment of side effects was similar, and we endeavored to provide optimal postoperative analgesia for each patient regardless of treatment group assignment within the confines of a double-blind study protocol.

In conclusion, our double-blind study demonstrates that the addition of ketorolac to fentanyl patient-controlled epidural analgesia provides significant im-

provements in postoperative pain management. Most importantly, patients in the ketorolac group had measurably better dynamic pain relief. Although not specifically measured in this study, improved dynamic pain relief would be expected to result in more frequent, extensive, and effective ambulation and pulmonary toilet, resulting in less postoperative morbidity. Another major benefit of the addition of ketorolac to fentanyl PCEA was the more rapid return of bowel function as measured by the return of bowel sounds and diet advancement. When the major determinant of postoperative length of hospitalization is return of bowel function, the addition of ketorolac to epidural opioid analgesia may result in significantly earlier discharge of patients and reduction of hospital costs.

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