Opioid-sparing Effects of Ketorolac and Its Correlation With the Recovery of Postoperative Bowel Function in Colorectal Surgery Patients

A Prospective Randomized Double-blinded Study

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Objectives: Postoperative ileus (PI) is one of many common complications in major abdominal surgery. PI results in patient discomfort, increased gastrointestinal leakage, prolonged hospital stay, and increased medical expenses. In this study, we have investigated the morphine-sparing effects of ketorolac and its correlation with the duration of PI in patients with colorectal surgeries.

Methods: We collected data from 102 patients who had received elective colorectal resection. The patients were randomly allocated into 2 groups and received intravenous patient-controlled analgesia (IVPCA) morphine (M group) or IVPCA morphine plus ketorolac (M + K group). Time-scale morphine consumption (per 12 h), recovery of bowel functions (the first bowel movement and passage of flatus), pain scores, and opioid-related side effects were then recorded.

Results: Patients in the M + K group received 18.3% less morphine than those in the M group within 72 postoperative hours. The maximal opioid-sparing effects of ketorolac appeared in 12 to 24 postoperative hours. The onset of the first bowel movement and passage of flatus was significantly less in the M + K group than in the M group. The M group showed a 5.25 times greater risk of inducing PI, a result comparable with the M + K group in colorectal surgery patients.

Discussion: The addition of ketorolac to IVPCA morphine has demonstrated a clear opioid-sparing effect and benefits in regards to the shortening of the duration of bowel immobility. We suggest that adding ketorolac to morphine IVPCA be included in the multimodal postoperative rehabilitation program for the early restoration of normal bowel function.

Key Words: postoperative ileus, patient-controlled analgesia, opioids, ketorolac

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Postoperative ileus (PI) is the transient impairment of bowel motility owing to surgical trauma and associated physiologic responses. The definition of PI duration is still controversial, though it is usually defined as the persistent gastrointestinal immobility in the 3 days after colorectal surgeries.[1] However, some authors have considered it to last longer.[2] Nevertheless, the duration of PI is much related to the anatomic location of surgery; for instance, colonic operations are often associated with the longest PI.[3] PI not only results in abdominal discomfort, nausea, vomiting, delayed oral intake, and increased postoperative morbidities,[4] but also increases medical expenditure. Therefore, resolving PI is still a significant healthcare problem.[5]

Opioids are the most effective drugs for the management of moderate-to-severe perioperative pain in the major abdominal surgeries.[6] However, their adverse effects have limited the use of them as analgesic agents. Among them, impaired bowel dysfunction is the most important and distressing adverse effect associated with opioid administrations in colorectal surgeries. Therefore, surgeons often limit the usage of postoperative opioids in fear of delayed recovery of bowel function. Although inflammatory responses have been proved to be one of the mechanisms contributing to PI,[7,8] anti-inflammatory drugs are seldom used to prevent PI in humans.[9,10] Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that possesses anti-inflammatory effects and opioid-sparing effects. It is often added to the opioid intravenous patient-controlled analgesia (IVPCA) to decrease opioid consumption during postoperative period. This prospective, randomized, double-blinded study was designed to test the opioid-sparing effects of ketorolac added to the IVPCA morphine in patients who received major colorectal surgeries.

MATERIALS AND METHODS

This study was conducted from June 2006 to June 2007 after gaining approval from the ethical committee of the hospital. One hundred and ten consecutive patients of the American Society of Anesthesiologists physical status I to III, with age ranging from 30 to 80 years, were included in this study upon obtaining their written informed consent. We calculated a sample size so that a between-group mean difference in the first 72 hours cumulative morphine consumption to the end point of the first passage of flatus would permit a type I error rate of $\alpha = 0.05$ with a power of 80%. This analysis indicated that a sample size of at least 47 patients/group was needed.

All patients received elective colorectal resections (Table 1) with simple anastomosis via midline incision by the same surgeon. This study excluded those who had a history of active peptic ulcer, poor renal function (serum creatinine > 1.3 mg/dL), preoperative coagulopathy (abnormal platelet count, prolonged bleeding time, prothrombin time, or activated partial thromboplastin time), previous history of allergy to morphine or ketorolac, opioid addiction, and inability to properly use patient-controlled analgesia (PCA) device. All participants were randomly allocated with the aid of computer-derived random number, and then received a verbal and written instruction to train on the use of the PCA device. These preoperative preparations were completed by 1 author on the preoperative day, who did not participate in any postoperative evaluation. Patients did not know the group allocations, and were divided into 2 different groups either receiving IVPCA (Amplus, Abbott) of morphine (M group) or morphine plus ketorolac (M + K group).

No opioids or NSAIDs were given 1 week before surgery and no premedication drugs were used preoperatively. All patients received prophylactic antibiotics 30 minutes before surgery. General anesthesia was induced with 3 to 5 mg/kg thiamylal and 2 to 5 μg/kg fentanyl intravenously. Endotracheal intubation was facilitated by 0.15 mg/kg cis-atracurium intravenously, and then patients were mechanically ventilated. Anesthesia was maintained with sevoflurane (at 1.5 to 2 MAC), and muscle relaxation was maintained with additional doses of cis-atracurium. A nasogastric tube was inserted after anesthesia had been established. Perioperative cardiovascular stability was maintained and blood transfusion was given when indicated. Every patient was sent to the postanesthetic care unit postoperatively where they immediately received a bolus of intravenous meperidine 50 to 100 mg for pain control. The dosage of meperidine was converted to morphine equivalents by a ratio of 7.5:1 and included in the 0 to 12 hours morphine consumption. Then, the PCA device was initiated. All the study drugs were prepared by the pharmacist and no label was put on the drug container. The 100 mL solution in the PCA reservoir bag contained 100 mg morphine with normal saline (1 mg/mL) in the M group or 100 mg morphine plus 120 mg ketorolac with normal saline (morphine 1 mg/mL, ketorolac 1.2 mg/mL) in the M + K group. The PCA setting was set at bolus of 2 mL with 10-minute lockout interval without continuous infusion for all patients. After discharge from postanesthetic care unit, all patients were visited every 6 hours by the acute pain service staff who were not aware of the patients' grouping. The pain service staff was trained to adjust the bolus dose by a 25% increase or decrease according to the patient's pain intensity on their daily visit. No other NSAIDs were given in the ward within the first 3 postoperative days. The use of PCA was discontinued when the visual analog scale (VAS, 0 = no pain, 10 = the worst intolerant pain) during movement was less than 3 in the following 2 consecutive evaluations.

The pain scores at rest and on movement were assessed with VAS. Nausea, vomiting, and the itching of skin were documented at each visit by the pain service staff. Morphine consumption was recalled from the PCA device records after withdrawing pain service. The time intervals from the end of surgery to the first bowel movement, the first passage of flatus, and the first ambulation (left bed and walked for at least 5 min) were recorded by the patients themselves, who then reported to our pain service staff. The ward care followed the clinical pathway of National Health Insurance system.

TABLE 1. Distribution of Surgical Types of Elective Colorectal Resections Between the 2 Groups

	M	M + K
Procedure		
Hemicolectomy	9	11
Abdominoperineal resection	11	10
Total colectomy	13	16
Sigmoid resection	18	15
Total	50	52

M indicates morphine; M + K, morphine plus ketorolac.

Statistics

Continuous variables are expressed as the mean ± SD and categorical variables are presented as frequencies (percentage of patients). Data were analyzed by χ^2 test for categorical variables and 2-tailed Student t test or Mann-Whitney U test for continuous variables when appropriate. Linear regression analysis of variance was performed by simple linear regression model procedure using SPSS (SPSS Institute Inc, Chicago, IL) for the correlation of PI with various predictors, including the addition of ketorolac, the first bowel movement, and time-scale morphine consumption. P value < 0.05 was defined as a significant difference.

RESULTS

Among the 110 participants, 102 patients completed the study course and were included in the statistical analysis. Of the 8 excluded cases, 3 patients in the M + K group and 1 patient in the M group received the second surgery owing to leakage from bowel anastomosis, 1 patient in the M group was transferred to the intensive care unit owing to respiratory failure unrelated to morphine use, and 2 patients (M group) had postoperative wound infection. There were no statistical differences in preoperative data between the 2 groups (Table 2).

Total morphine consumption of the first 3 days was significantly lower in the M + K group (66.0 ± 32.5 mg in the M + K group vs. 80.8 ± 32.6 mg in the M group) (Fig. 1). We noticed that adding ketorolac in the intravenous morphine PCA presented the significant opioid-sparing effect in the first and second 12 postoperative hours. Nevertheless, the morphine consumption in the following several 12-hour intervals was not significantly different between the 2 groups. There were significant differences in the time to the first bowel movements between the 2 groups (1.8 ± 1.0 d in the M + K group vs. 2.4 ± 1.1 d in the M group) and the time to the first passage of flatus (3.3 ± 1.3 d in the M + K group vs. 4.0 ± 1.2 d in the M group) (Table 3). However, no significant differences between the 2 groups were found in the rest pain score or the worst pain scores except the movement VAS on the third postoperative day (Table 2). Operation time, amount of bleeding, the duration of PCA use, and opioid-induced adverse effects were also not significantly different between the 2 groups (Tables 2 and 4) (Fig. 2).

TABLE 2. Demographic Data and Pain Score of the Patients

	M	M + K	*P*
Male/female	30/20	23/29	0.12
Age	60.5 ± 12.2	57.3 ± 11.6	0.13
Weight (kg)	62.2 ± 12.4	58.7 ± 11.2	0.20
Height (cm)	160.5 ± 6.9	159.3 ± 8.5	0.59
Blood loss	133.0 ± 126.8	130.8 ± 231.8	0.20
Operation time (min)	271.6 ± 74.8	244.3 ± 60.8	0.08
PCA (d)	6.1 ± 1.3	6.0 ± 0.8	0.70
VAS at rest			
First POD	2.0 ± 1.3	1.7 ± 1.2	0.20
Second POD	1.2 ± 1.1	1.1 ± 1.9	0.67
Third POD	0.9 ± 0.9	0.7 ± 1.0	0.41
VAS on movement			
First POD	4.6 ± 1.5	4.4 ± 1.4	0.45
Second POD	3.9 ± 1.3	3.5 ± 1.1	0.08
Third POD	3.4 ± 1.1	2.9 ± 1.0	0.03*

Values are presented as mean ± SD.
*$P < 0.05$.
M indicates morphine; M + K, morphine plus ketorolac; PCA, patient-controlled analgesia; POD, postoperative day; VAS, visual analog scale.

TABLE 3. Postoperative Bowel Function and Morphine Consumption Every 12 Hours

	M	M + K	*P*
Bowel movement (d)	2.4 ± 1.1	1.8 ± 1.0	< 0.001*
Flatus (d)	4.0 ± 1.2	3.3 ± 1.3	0.01*
Mobilization (d)	2.3 ± 1.1	2.1 ± 1.0	0.34
$MC_{1\text{-}12\,h}$ (mg)	23.6 ± 11.8	18.9 ± 9.3	0.027*
$MC_{12\text{-}24\,h}$ (mg)	17.8 ± 9.1	12.5 ± 7.2	0.001*
$MC_{24\text{-}36\,h}$ (mg)	12.3 ± 7.3	10.3 ± 6.5	0.138
$MC_{36\text{-}48\,h}$ (mg)	11.7 ± 6.9	10.3 ± 5.6	0.259
$MC_{48\text{-}60\,h}$ (mg)	7.7 ± 5.6	7.3 ± 4.7	0.763
$MC_{60\text{-}72\,h}$ (mg)	7.7 ± 4.9	6.7 ± 4.2	0.241
$MC_{0\text{-}24\,h}$ (mg)	41.4 ± 17.9	31.4 ± 14.2	< 0.001*
$MC_{24\text{-}48\,h}$ (mg)	24.0 ± 12.5	20.6 ± 10.9	0.14
$MC_{48\text{-}72\,h}$ (mg)	15.4 ± 9.6	14.0 ± 7.4	0.42
$MC_{0\text{-}48\,h}$ (mg)	65.5 ± 26.7	52.0 ± 22.8	0.01*
$MC_{0\text{-}72\,h}$ (mg)	80.8 ± 32.6	66.0 ± 27.8	0.01*

Values are presented as mean ± SD.
*$P < 0.05$.
M indicates morphine; M + K, morphine plus ketorolac; $MC_{x\text{-}y\,h}$, morphine consumption from x to y hours.

To have better understanding of the impact of adding ketorolac in the intravenous morphine PCA utilization on postoperative bowel functions, we also analyzed the correlation between morphine consumption every 12 hours and the duration of PI. We defined the first passage of flatus within 3 postoperative days as the normal group, and the first passage of flatus beyond 5 postoperative days as the abnormal group, and tried to compare the PI predictors. We found that the M group had a 5.25 times more risk to prolong the duration of PI for 1 day when compared with the M + K group in colorectal surgery patients. There was significantly positive correlation between the flatus and bowel movement too. However, simple linear regression analysis showed no significant correlation between the first passage of flatus and morphine consumption every 12 hours (Table 5).

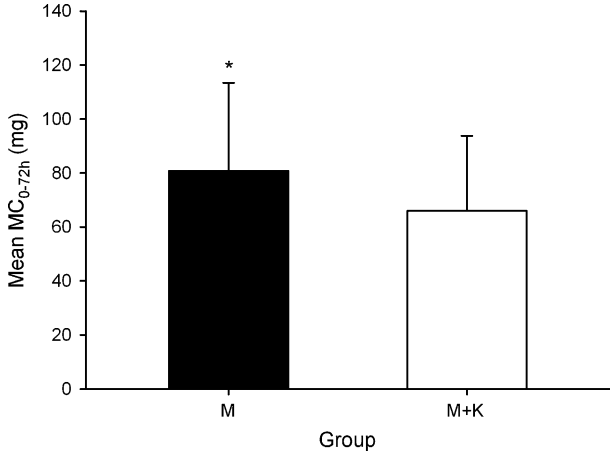

FIGURE 1. Total morphine consumption between groups was significantly different. Ketorolac addition could reduce the total morphine consumption as much as 18.3%. Error bar indicates SD; M, morphine group; MC, morphine consumption; M+K, morphine plus ketorolac group. *$P<0.05$.

DISCUSSION

In this study, we demonstrated the opioid-sparing effects of ketorolac. The morphine consumption of the first 3 days was decreased by 18.3% in the M + K group. The addition of ketorolac in IVPCA morphine benefited the patients after colorectal surgery by shortening their recovery duration of postoperative bowel movement and passage of flatus. The positive correlation between PI and morphine dosage found in this study implied that the effect of opioids on bowel mobility existed, but this correlation was not significant enough to become one of the PI predictors. Relatively, the effects of adding ketorolac in the intravenous morphine PCA in the M + K group could prevent PI, as compared with the M group in this study. In addition, the opioid-sparing effect of ketorolac provided effective analgesic effect equivalent to morphine group and did not increase the incidence of NSAIDs-related side effects.

To assess the reduction in morphine consumption by adding ketorolac in the postoperative period, we found that the reduction in morphine consumption in the first 3 days was in the range of 5% to 25% during the time-scale interval. Meanwhile, we noticed that major opioid-sparing effects occurred on the first day. On the other hand, the second and third day did not show significant reduction in morphine consumption. It was speculated that ketorolac should be held from PCA after the first day use, if there were any hazards concerning the side effects of NSAIDs.

TABLE 4. Side Effects of PCA Between Groups

	Group	Mild	Moderate	Severe	Total (%)	*P*
Pruritus	M	9	5	1	15 (30)	0.30
	M + K	8	3	0	11 (21.2)	
Nausea and vomiting	M	11	1	1	12 (24)	0.27
	M + K	6	2	0	8 (15.4)	
Dizziness	M	7	4	0	11 (22)	0.55
	M + K	8	2	0	10 (19.2)	

M indicates morphine; M + K, morphine plus ketorolac; PCA, patient-controlled analgesia.

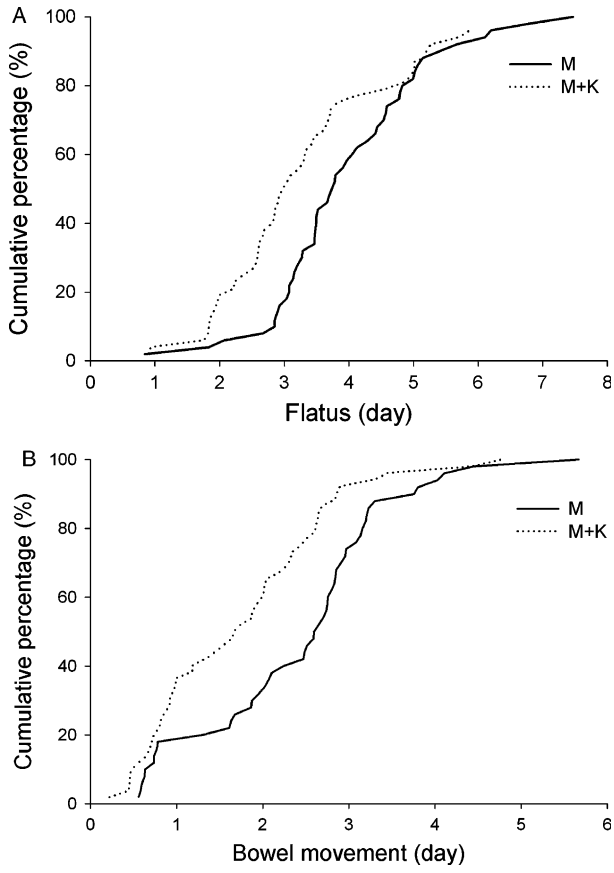

FIGURE 2. The cumulative percentage of the first passage of flatus time (A) and the first bowel movement time (B) in both groups. M indicates morphine group; M+K, morphine plus ketorolac group.

Although many studies have shown that epidural analgesia with local anesthetics or opioids are superior to intravenous opioids PCA in the early recovery of postoperative bowel function,[11,12] epidural catheterization does carry certain risks owing to its invasiveness, for example, motor blockade, postdural puncture headache, nerve injury, and meningitis.[13–15] In contrast, IVPCA has the benefits of convenience, less technical difficulties, and less potential risks. In Asia, IVPCA is more acceptable because of the incorrigible fear of potential neurologic sequelae after spinal interventions such as spinal surgeries, spinal tapping, or injections. This study provides a confirmative, evidence-based alternative of choices for postcolorectal surgical pain management.

Many drugs had been combined with opioids to decrease opioids consumption and minimize their undesired side effects, including NSAIDs, *N*-methyl-D-aspartic acid receptors antagonists, and selective receptor agonists have been administered with opioids because of the well-known opioid-sparing effects.[16] Ketorolac is the one of NSAIDs that possesses anti-inflammatory effects and opioid-sparing effects.[17] During PI, there is an activation of resident immune cells, particularly macrophages, and the recruitment of circulating leukocytes to the bowel wall. A cytokine cascade ultimately leads to muscle dysfunction with a pivotal role for tumor necrosis factor-α and interleukin-1β. Prostaglandins are implicated in this inflammatory response and inhibition of intestinal smooth muscle function.[18,19] Ketorolac is added to intravenous opioid PCA to decrease opioid consumption during the postoperative period. We tried to verify that the ketorolac could enhance the recovery of postoperative bowel function; however, more clinical trials are needed to prove this conjecture.

TABLE 5. Simple Logistic Regression

	Exp (B)	95% CI	*P*
Group			
M	5.25	2.07-13.32	< 0.001*
M + K	1.00		
Bowel movement	2.22	1.40-3.51	0.001*
Mobilization	1.32	0.86-2.02	0.20
$MC_{1\text{-}12\,h}$	0.98	0.94-1.01	0.23
$MC_{12\text{-}24\,h}$	0.98	0.93-1.03	0.38
$MC_{24\text{-}36\,h}$	0.95	0.90-1.01	0.09
$MC_{36\text{-}48\,h}$	0.96	0.90-1.02	0.19
$MC_{48\text{-}60\,h}$	1.00	0.92-1.08	0.93
$MC_{60\text{-}72\,h}$	0.97	0.88-1.06	0.44
$MC_{0\text{-}24\,h}$	0.99	0.96-1.01	0.23
$MC_{24\text{-}48\,h}$	0.97	0.94-1.01	0.09
$MC_{48\text{-}72\,h}$	0.99	0.94-1.04	0.64
$MC_{0\text{-}48\,h}$	0.99	0.97-1.00	0.12
$MC_{0\text{-}72\,h}$	0.99	0.98-1.00	0.16

*Significant at the 0.05 level (2-tail).

Dependent variable indicates flatus within 3 days (normal) and flatus beyond 5 postoperative days (abnormal).

CI indicates confidence interval; Exp (B), logistic coefficient of Simple linear regression; M, morphine; M + K, morphine plus ketorolac; MC, morphine consumption.

Kelley et al[9] showed that ketorolac could benefit postoperative small intestinal ileus of rats in 1993, but no human data are available after that. Recently, some studies focused on the role of inflammatory mediator in PI.[8,20,21] Sim et al[10] also showed that valdecoxib, a cyclooxygenase-2 specific inhibitor, reduced the duration of PI in patients undergoing major colorectal surgery. Unfortunately, the cyclooxygenase-2 specific inhibitor was withdrawn from the market owing to its cardiovascular toxicity in many countries. Therefore, ketorolac seemed to be a much safer choice for patients receiving major colorectal surgery.

Opioids have been reported to act at spinal and cerebral opioid receptors and suppress pain transmission. They also inhibit gut motility and decrease intestinal secretory function at the level of myenteric plexus.[6] In this study, we have found that the morphine consumption did not show significant correlation with either flatus passage or bowel movement. We thought that the recovery of postoperative bowel function was related to multiple factors, such as inflammatory responses, surgical pain, and sympathetic hyperactivity.[22] The effect of opioids may not be a crucial factor. The multimodal postcolorectal surgical program to reduce the duration of PI has been advocated, and includes minimally invasive laparoscopic surgery, epidural anesthesia, reduction of opioid use, early mobilization, enteral feeding, prokinetic agents, and nasogastric suction.[23–25] We suggest that adding ketorolac to intravenous morphine PCA can be included in the multimodal postoperative rehabilitation program for early restoration of normal bowel function if IVPCA is indicated for postoperative pain management in colorectal surgeries.

In conclusion, this randomized, double-blind study demonstrated that adding ketorolac to intravenous morphine PCA could shorten the duration of PI. It seemed that the opioid-sparing effect could not explain the whole panorama. PI seems to be a multifactorial problem and the opioid-induced impairment of bowel function may be overemphasized. We advocate that ketorolac should be considered if the intravenous morphine PCA is used in the colorectal surgery patients.

REFERENCES

1. Prasad M, Matthews JB. Deflating postoperative ileus. *Gastroenterology*. 1999;117:489–492.
2. Artinyan A, Nunoo-Mensah JW, Balasubramaniam S, et al. Prolonged postoperative ileus: definition, risk factors, and predictors after surgery. *World J Surg*. 2008;32:1495–1500.
3. Holte K, Kehlet H. Postoperative ileus: a preventable event. *Br J Surg*. 2000;87:1480–1493.
4. Kehlet H. Postoperative ileus. *Gut*. 2000;47(suppl 4):485–486.
5. Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Am J Health Syst Pharm*. 2007;64:S3–S37.
6. Friedman JD, Dello Buono FA. Opioid antagonists in the treatment of opioid-induced constipation and pruritus. *Ann Pharmacother*. 2001;35:85–91.
7. The FO, Bennink RJ, Ankum WM, et al. Intestinal handling-induced mast cell activation and inflammation in human postoperative ileus. *Gut*. 2008;57:33–40.
8. Wehner S, Behrendt FF, Lyutenski BN, et al. Inhibition of macrophage function prevents intestinal inflammation and postoperative ileus in rodents. *Gut*. 2007;56:176–185.
9. Kelley MC, Hocking MP, Marchand SD, et al. Ketorolac prevents postoperative small intestinal ileus in rats. *Am J Surg*. 1993;165:107–112.
10. Sim R, Cheong DM, Wong KS, et al. Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific inhibitor as opioid-sparing analgesia in major colorectal surgery. *Colorectal Dis*. 2007;9:52–60.
11. Rigg JR, Jamrozik K, Myles PS, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet*. 2002;359:1276–1282.
12. Carli F, Trudel JL, Belliveau P. The effect of intraoperative thoracic epidural anesthesia and postoperative analgesia on bowel function after colorectal surgery: a prospective, randomized trial. *Dis Colon Rectum*. 2001;44:1083–1089.
13. Hayek SM, Paige B, Girgis G, et al. Tunneled epidural catheter infections in noncancer pain: increased risk in patients with neuropathic pain/complex regional pain syndrome. *Clin J Pain*. 2006;22:82–89.
14. Sidiropoulou T, Pompeo E, Bozzao A, et al. Epidural hematoma after thoracic epidural catheter removal in the absence of risk factors. *Reg Anesth Pain Med*. 2003;28:531–534.
15. Horlocker TT, Abel MD, Messick JM Jr, et al. Small risk of serious neurologic complications related to lumbar epidural catheter placement in anesthetized patients. *Anesth Analg*. 2003;96:1547–1552; table of contents.
16. Lu CH, Liu JY, Lee MS, et al. Preoperative cotreatment with dextromethorphan and ketorolac provides an enhancement of pain relief after laparoscopic-assisted vaginal hysterectomy. *Clin J Pain*. 2006;22:799–804.
17. Kim MH, Hahm TS. Plasma levels of interleukin-6 and interleukin-10 are affected by ketorolac as an adjunct to patient-controlled morphine after abdominal hysterectomy. *Clin J Pain*. 2001;17:72–77.
18. Mueller MH, Glatzle J, Kampitoglou D, et al. Differential sensitization of afferent neuronal pathways during postoperative ileus in the mouse jejunum. *Ann Surg*. 2008;247:791–802.
19. Korolkiewicz RP, Ujda M, Dabkowski J, et al. Differential salutary effects of nonselective and selective COX-2 inhibitors in postoperative ileus in rats. *J Surg Res*. 2003;109:161–169.
20. De Giorgio R, Barbara G. Evidence for mast cell involvement in human postoperative ileus: a novel link. *Gut*. 2008;57:5–7.
21. Moore BA, Albers KM, Davis BM, et al. Altered inflammatory gene expression underlies increased susceptibility to murine postoperative ileus with advancing age. *Am J Physiol Gastrointest Liver Physiol*. 2007;292:G1650–G1659.
22. Bauer AJ, Boeckxstaens GE. Mechanisms of postoperative ileus. *Neurogastroenterol Motil*. 2004;16(suppl 2):54–60.
23. Gannon RH. Current strategies for preventing or ameliorating postoperative ileus: a multimodal approach. *Am J Health Syst Pharm*. 2007;64:S8–S12.
24. Holte K, Kehlet H. Postoperative ileus: progress towards effective management. *Drugs*. 2002;62:2603–2615.
25. Kehlet H, Holte K. Review of postoperative ileus. *Am J Surg*. 2001;182:3S–10S.