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Effect of adding ketorolac to intravenous morphine patient-controlled analgesia on bowel function in colorectal surgery patients – a prospective, randomized, double-blind study

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Background: Postoperative ileus (PI) is the transient impairment of bowel motility due to surgical trauma and the associated physiological responses. Postoperative ileus results in patient discomfort, increases gastrointestinal risks, prolongs hospital stay and increases medical expenses. In this study, we investigated the effect of patient-controlled analgesia (PCA) morphine with or without ketorolac on bowel functions in patients after colorectal surgeries.
Methods: A total of 79 patients who received elective colorectal resection were randomly allocated into two groups receiving either intravenous PCA morphine (M group) or intravenous PCA morphine plus ketorolac (K group). Recovery of bowel functions (bowel movement, passage of flatus, and soft diet intake), pain scores, morphine consumption, time for first ambulation, and opioid-related side-effects were recorded.
Results: Patients in the K group received 29% less morphine than patients in the M group with comparable pain scores. The first bowel movement (1.5 [0.7–1.9] vs. 1.7 [1.0–2.8] days, $P < 0.05$) and the first ambulation (2.2 ± 1.0 vs. 2.8 ± 1.2 days, $P < 0.05$) were significantly earlier in the K group than in the M group. The time of the first flatus passing, the first intake of soft diet, and duration of hospital stay were not significantly different between the two groups.
Conclusions: The results of this study suggest that addition of ketorolac to intravenous morphine PCA provides an opioid-sparing effect but has limited benefit in shortening the duration of bowel immobility and time to first ambulation. These findings imply that postoperative ileus is attributable to multiple factors in addition to morphine consumption.

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Key words: Bowel movement; ketorolac; opioids; patient-controlled analgesia; postoperative ileus; postoperative pain.

POSTOPERATIVE ileus (PI) is one of the common complications after abdominal surgery. It is usually defined as persistent bowel immobility for more than 3 days after surgery (1). Postoperative ileus not only results in abdominal discomfort, nausea, vomiting, delayed oral intake, and increase postoperative morbidity (2), but also prolongs the hospital stay and increases medical costs (3, 4). Prolonged recovery of postoperative gastrointestinal functions remains a significant healthcare problem (5).

Opioids are effective for the management of moderate to severe perioperative pain in major abdominal surgery (1, 6). However, adverse effects can compromise the usefulness of these agents for analgesia. Bowel dysfunction is among the most important and distressing adverse effects associated with opioid administration. The use of opioids in the postoperative period after bowel surgery has been viewed as a double-edged sword with the benefit of pain relief on one hand and the impairment of bowel function on the other. Thus surgeons often limit the usage of postoperative opioids for fear of prolonged recovery of bowel function. However, somewhat surprisingly, only a few studies have investigated the correlation between postoperative opioids and PI (7–11), and most of them involved epidural opioids and non-gastrointestinal surgeries. Only one previous study has investigated the effect of morphine dose on PI in

colorectal surgery (12), but it did not investigate the influence of changing morphine formulation on PI. This is the first prospective, randomized, double-blind study to test the hypothesis that the opioid-sparing effect of the addition of ketorolac in patient-controlled analgesia (PCA) morphine can shorten the duration of PI and hospitalization after major colorectal surgery.

Methods

This prospective, randomized double-blind study was conducted from January 2003 to December 2003 after approval was obtained from the Shin Kong Wu Ho-Su Memorial Hospital Ethics Committee. Seventy-nine consecutive patients with American Society of Anesthesiologists (ASA) physical status I or II, with age ranging from 35 to 75 years, participated in this study after giving written informed consent. We calculated a sample size so that a between-group mean difference in cumulative morphine consumption to the endpoint of the first bowel movement would permit a type I error rate of 0.05 in a one-tailed test of significance with a power of 80%. This analysis indicated that a sample size of at least 32 patients per group was needed.

All patients received elective colorectal resections (Table 1) with simple anastomosis via midline incision by the same surgeon (Y.H. Chou). Exclusion criteria included active peptic ulcer, poor renal function (serum creatinine over 1.5 mg dl^{-1}), 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 the PCA device. All subjects received a written instruction and verbal training on the use of the PCA device, and then were randomly allocated to their treatment group with the aid of computer-derived random number. These preoperative preparations were completed on the day before the surgery by one author (W.S. Chan) who did not personally participate in the postoperative evaluation. Patients received PCA (Abbot aim® plus, Abbot Laboratories, Norton Chicago, IL) with either intravenous morphine (M group) or intravenous morphine combined with ketorolac (K group), without knowledge of their group allocation.

Table 1

Distribution of types of elective colorectal surgical procedures in the two groups.

Procedure	M Group	K Group
Hemicolectomy	5	4
Abdominoperineal resection	8	7
Total colectomy	7	9
Sigmoid resection	15	19
Total	35	39

No opioids or non-steroidal anti-inflammatory drugs (NSAIDs) were given within 1 week before surgery and no premedication drugs were used preoperatively. All patients received prophylactic antibiotics at 30 min before surgery. General anesthesia was induced with 3–5 mg kg^{-1} thiamylal and 2–4 μg kg^{-1} fentanyl intravenously (i.v.). Endotracheal intubation was facilitated by 0.15 mg kg^{-1} *cis*-atracurium i.v., and patients were mechanically ventilated. Anesthesia was maintained with sevoflurane (at 1.5–2 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 post-anesthetic care unit postoperatively where they immediately received a bolus of intravenous meperidine 50–100 mg for pain control. Then, the use of the PCA device was initiated. All the study drugs were prepared by a pharmacist and no label was put on the PCA reservoir bag. The 100-ml solution in the PCA reservoir bag contained 100 mg of morphine in normal saline (1 mg ml^{-1}) in the M group or 100 mg morphine plus 120 mg of ketorolac in normal saline (morphine 1 mg ml^{-1}; ketorolac 1.2 mg ml^{-1}) in the K group. The PCA setting was set at a bolus of 2 ml with a 10-min lockout interval without a continuous infusion for all patients. After discharge from the PACU, all patients were visited twice per day by acute pain service staff who were not aware of the patients' grouping. The pain service staff were trained to adjust the bolus dose by a 20–50% increase or a 20–25% decrease according to the patient's pain intensity at the time of the daily visit. No other NSAIDs were given on the ward postoperatively. The use of PCA was discontinued when VAS on movement was less than 3 on two consecutive evaluations.

The pain scores at rest and on movement were assessed with the visual analog scale (VAS, 0 = no pain, 10 = the worst intolerant pain). Morphine consumption, doses of rescue analgesic (meperidine), nausea, vomiting, skin itching, and sedation at the time of each visit were documented. The time intervals from the end of surgery to the first bowel movement and to the first flatus were recorded by the patients. Data on the time to the first ambulation

(left bed and walked for at least 5 min) and to the first intake of soft diet (standard hospital formula permitted by the surgeon) were specifically asked and recorded by the pain service staff. Data on the duration of hospitalization after surgery were collected from the patient's medical record after the patient was discharged.

Statistics

Continuous variables are expressed as the mean ±standard deviation or median (25th to 75th percentile) when data were not normally distributed, and categorical variables are presented as frequencies (percentage of patients). Data were analyzed by chi-square test for categorical variables and two-tailed Student's *t*-test or Mann–Whitney *U*-test for continuous variables. A *P*-value < 0.05 was considered to indicate a significant difference.

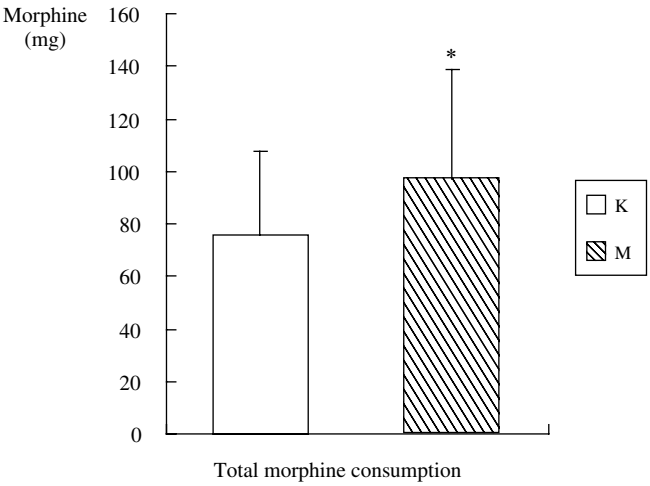

*Fig. 1. Ketorolac addition was associated with a 29% reduction in total morphine consumption. (M: morphine group; K: morphine plus ketorolac group; error bar = standard deviation; *P < 0.05).*

Results

Among the 79 participants, 74 patients completed the study course and were included in the analysis. Of the five excluded patients, two in the K group and one in the M group received second surgeries due to leakage from bowel anastomosis, one patient in the M group was transferred to the intensive care unit due to respiratory failure unrelated to morphine use, and one patient in the M group had postoperative wound infection. There were no differences in preoperative data between the two groups (Table 2).

Total morphine consumption was significantly lower in the K group (71.4 [55.0–96.1] mg) than in the M group (93.3 [70.4–127.1] mg) (Fig. 1). The respective cumulative morphine doses from the end of surgery to the first bowel movement and to the first passage of flatus were also significantly lower in the K group than in the M group (28.0 [18.0–44.0] mg in the K group vs. 57 [34.5–69.8] mg in the M group for bowel movement; 51.5 [38.0–71.2] mg in the K group vs. 75.5 [60.8–93.3] mg in the M group for flatus). There were significant differences between the two groups in the time to the first bowel movement (1.5 [0.7–1.9] days in the K group vs. 1.7 [1.0–2.8] days in the M group) and the time to the first ambulation (2.2 ± 1.0 days in the K group vs. 2.8 ± 1.2 days in the M group) (Fig. 2). However, no significant differences were found in the time to the first flatus, the time to the first soft diet, and the number of postoperative hospitalization days between the two groups (Fig. 2). Duration of surgery, amount of bleeding, the duration of PCA use, postoperative pain scores, rescue meperidine dose and opioid-induced adverse effects were also similar between the two groups (Tables 3 and 4).

Discussion

This study suggests that the addition of ketorolac in intravenous PCA provides benefits in patients after colorectal surgery in reducing the total amount of morphine consumption, shortening the duration of

Table 2

Demographic characteristics and operative data of the patients.

Group	Mean ± SD or median (25th–75th percentile)		*P*
	M	K	
Male/Female	22/13	19/20	0.22
Age	68 (47.8–74.0)	64.5 (48.5–71.0)	0.51
Weight (kg)	61 ± 13.4	61.1 ± 10.9	0.91
Height (cm)	161.1 ± 8.8	161.7 ± 8.1	0.78
Operation time (h)	4.0 ± 1.1	3.7 ± 1.2	0.38
Amount of bleeding (ml)	111 ± 85	88 ± 63	0.26
Rescue meperidine dose (mg)	60 ± 41	67 ± 52	0.47

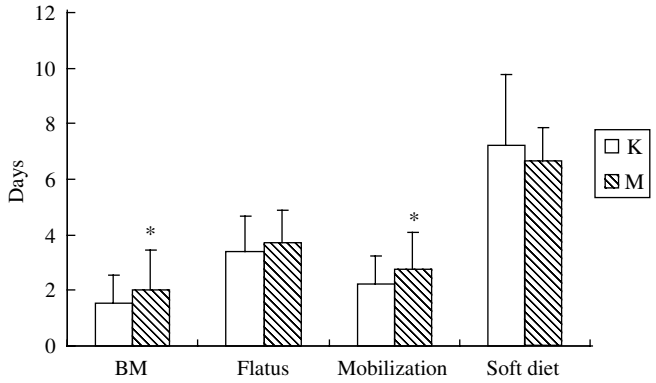

*Fig. 2. Duration from the end of surgery to the first bowel movement, the first passage of flatus, the first mobilization, and the first soft diet feeding (M: morphine group; K: morphine plus ketorolac group; BM: bowel movement; error bar = standard deviation; *P < 0.05).*

recovery of postoperative bowel movement and ambulation. The duration to the first flatus, to the first soft diet, and postoperative hospital stay in the morphine-ketorolac group was decreased but were not significantly different from those in the morphine group. The opioid-sparing effect of ketorolac was provided without loss of analgesia and did not increase NSAID-related side-effects.

Postoperative ileus is of particular concerned to surgeons. Ileus can cause abdominal discomfort, nausea and vomiting. More importantly, it delays return of bowel function and the resumption of oral intake, resulting in prolonged hospitalization (3). Use of opioids for postoperative pain could act at the spinal and cerebral opioid receptors and suppress pain transmission, but it also inhibits gut motility and decreases intestinal secretory function at the level of myenteric plexus (6). Increasing the morphine dose significantly delays transit time in the small bowel and colon (13), the time to first audible bowel sound, to the passage of flatus, and to the first bowel movement (12). However, morphine did not delay the recovery of bowel function after abdominal surgery if given in small doses by intravenous PCA (14). In our study, morphine consumption had limited impact on PI recovery, which suggests there may be a certain range of morphine escalation within which there would be no significant inhibition of bowel motility. Among patients in the M group, the average time to flatus passage was not prolonged despite a 29% higher morphine dose than patients in the K group. This suggests that the existence and severity of surgical pain are the important indicators of the need for increasing the morphine dose to relieve pain or decreasing the dose to avoid PI.

In addition to the opioid effect, multiple factors like surgical pain, bowel inflammation and sympathetic hyperactivity are involved in bowel movement (7). A multimodal postcolorectal surgical program to reduce the PI has been advocated which included minimally invasive laparoscopic surgery, epidural anesthesia, reduction of opioid use, early mobilization, enteral feeding, prokinetic agents, and nasal-gastric suction (2, 5, 15, 16). Recent studies demonstrated that under the program, PI and hospital stay were substantially shortened (17). We did not adopt such a rehabilitation program, but continued with a conventional perioperative care technique because the National Health Insurance system in Taiwan lacks a compulsory clinical pathway for major surgeries and allows substantial variability in the surgical program. Nevertheless, this study suggests that a simple combination analgesic regimen can provide advantages over single opioid treatment in PI under such conditions, which we believe is of reference value to our colleagues in other countries in the world.

In assessing the additive effect of ketorolac, our results showed a reduction of total morphine consumption by 29% which is comparable to other

Table 3

Duration of patient-controlled analgesia use, data on visual analog scale pain, and duration of hospital stay.

Group	Median (25th–75th percentile)		*P*
	M	K	
Duration of PCA-treatment (days)	5.7 (5.4-6.5)	5.8 (4.9-6.0)	0.57
VAS at rest			
1st POD	2.5 (1.9-2.6)	2.2 (1.9-2.5)	0.65
2nd POD	2.0 (1.7-2.3)	1.9 (1.4-2.1)	0.10
3rd POD	1.4 (1.3-1.8)	1.3 (1.1-1.8)	0.39
VAS on movement			
1st POD	4.4 (4.0-4.7)	4.5 (4.0-4.9)	0.91
2nd POD	4.1 (3.7-4.4)	4.0 (3.6-4.4)	0.90
3rd POD	3.6 (3.2-3.9)	3.4 (3.2-4.0)	0.91
Hospital stay (days)	15 (14.0-19.3)	14.5 (12.0-20.0)	0.73

PCA = patient-controlled analgesia; VAS = visual analog scale; POD = postoperative day.

Table 4

Side-effects of patient-controlled analgesia in the two groups.

	Group	Mild	Moderate	Severe	Total (%)
Pruritus	M	6	3	1	10 (28.5)
	K	8	2	0	10 (25.6)
Nausea or vomiting	M	7	1	1	9 (25.7)
	K	6	1	0	7 (17.9)
Dizziness	M	4	0	0	4 (11.4)
	K	4	0	0	4 (10.2)

studies reporting that ketorolac addition could reduce morphine consumption by 25% to 45% (18–20). Clinical assessment of the recovery from PI is difficult because there is a lack of consensus on a reliable endpoint for use by the surgeon. The passage of flatus reported by patients is a good clinical sign and is frequently used (21), but the correlation between flatus and bowel movement is questionable (9). Others have advocated that time to first bowel movement is a more reliable and sensitive endpoint indicating the return of bowel motility (10). Studies have strongly suggested that early oral feeding is safe and tolerated well by the majority of patients (11, 22); however, we waited for the resolution of ileus to initiate the feeding. This probably resulted in delayed oral intake and hospital discharge, and obscured the difference between the groups with or without ketorolac.

Although many studies have shown that epidural analgesia with local anesthetics or combination of local anesthetics and opioids is superior to intravenous PCA in the earlier recovery of postoperative bowel function (23, 24), epidural catheterization does carry certain risks due to its invasiveness, e.g. motor blockade, postdural puncture headache, nerve injury, and meningitis. The inhibitory effect on bowel motility is not completely avoided with epidural analgesia (25). On the other hand, intravenous PCA has the benefits of convenience, less technical difficulties, and less potential risks. In Asia, especially for the Chinese, intravenous PCA is more acceptable because of the incorrigible fear of potential neurological sequelae following spinal interventions like spinal surgeries, spinal tapping, or injections. Besides, the addition of adjuncts in intravenous morphine could ameliorate some of the opioid-related adverse effects like somnolence, nausea and vomiting as well as enhance analgesia (8, 18).

In conclusion, this randomized, double-blind study reports that adding ketorolac in intravenous morphine PCA provides an opioid-sparing effect but only mildly shortens the duration of postoperative bowel immobility in colorectal surgery patients. Postoperative ileus appears to be a multifactorial problem, and opioid-induced impairment of bowel function might be overemphasized. A multimodal postoperative rehabilitation program aiming at multiple mechanisms affecting postoperative ileus would improve the early restoration of normal bowel functions.

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