Surg Endosc (2007) 21: 2212–2219
DOI: 10.1007/s00464-007-9335-4

SURGICAL ENDOSCOPY
and Other Interventional Techniques

Optimizing recovery after laparoscopic colon surgery (ORAL-CS)

Effect of intravenous Ketorolac on length of hospital stay

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Received: 18 October 2006/Accepted: 4 December 2006/Online publication: 13 April 2007

Abstract
Background: The objective of this study was to determine if intravenous ketorolac can reduce ileus following laparoscopic colorectal surgery, thus shortening hospital stay.
Methods: This was a prospective, randomized, double-blind, placebo-controlled, clinical trial of patients undergoing laparoscopic colorectal resection and receiving morphine patient controlled analgesia (PCA) and either intravenous ketorolac (group A) or placebo (group B), for 48 h after surgery. Daily assessments were made by a blinded assistant for level of pain control. Diet advancement and discharge were decided according to strictly defined criteria.
Results: From October 2002 to March 2005, 190 patients underwent laparoscopic colorectal surgery. Of this total, 84 patients were eligible for this study and 70 consented. Another 26 patients were excluded, leaving 22 patients in each group. Two patients who suffered anastomotic leaks in the early postoperative period were excluded from further analysis. Median length of stay for the entire study was 4.0 days, with significant correlation between milligrams of morphine consumed and time to first flatus ($r = 0.422$, $p = 0.005$), full diet ($r = 0.522$, $p < 0.001$), and discharge ($r = 0.437$, $p = 0.004$). There we no differences between groups in age, body mass index, or operating time. Patients in group A consumed less morphine (33 ± 31 mg versus 63 ± 41 mg, $p = 0.011$), and had less time to first flatus (median 2.0 days versus 3.0 days, $p < 0.001$) and full diet (median 2.5 days versus 3.0 days, $p = 0.033$). The reduction in length of stay was not significant (mean 3.6 days versus 4.5 days, median 4.0 days versus 4.0 days, $p = 0.142$). Pain control was superior in group A. Three patients required readmission for treatment of five anastomotic leaks (4 in group A versus 1 in group B, $p = 0.15$). Two of them underwent reoperation.
Conclusions: Intravenous ketorolac was efficacious in improving pain control and reducing postoperative ileus when anastomotic leaks were excluded. This simple intervention shows promise in reducing hospital stay, although the outcome was not statistically significant. The high number of leaks is inconsistent with this group's experience and is of concern.

Key words: Laparoscopy — Colon surgery — Laparoscopic colon surgery — Intestinal ileus — Fast-track — NSAIDs — Ketorolac — Patient-controlled analgesia

Laparoscopic surgery has dramatically changed the face of general surgery over the past decade especially in terms of diminished length of hospital stay. Laparoscopic cholecystectomy has become predominantly an outpatient procedure. Laparoscopic splenectomy, adrenalectomy, and anti-reflux procedures are usually associated with only 1- or 2-day hospital admissions.

In several prospective randomized trials, laparoscopic colon resection resulted in a shorter length of hospital stay as compared to open colon resection [9, 12, 14, 18, 19, 22, 25]. However, in these trials an average hospital stay of 5 or more days is still required, due primarily to postoperative ileus and the length of time required for the resumption of normal intestinal activity.

Multimodal strategies of early ambulation, early feeding, minimizing opioid analgesia, and use of thoracic epidural have been shown by some investigators to lead to impressive improvements in duration of hospital

This paper was presented at the 2006 SAGES Annual Meeting, April 28, 2006, Dallas, Texas

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stay [17], but these results have not been widely reproduced. Additionally, there is some doubt as to the value of epidural analgesia as compared to patient controlled analgesia (PCA) in this patient population [15, 26].

The current standard for pain management after open colon resection is PCA [1]. The ideal postoperative pain management regimen for laparoscopic colectomy has not been elucidated. This reliance on opioids is obviously a reflection of postoperative pain management for open colon resection. Laparoscopic colon resection results in less postoperative pain, presumably because it is performed through smaller incisions, leading to an overall diminished traumatic insult [23]. Nonsteroidal anti-inflammatory medications (NSAID) have been used extensively in postoperative pain management because they avoid many of the undesirable effects of opioids such as respiratory depression, sedation, hallucinations, euphoria, dependence, decreased intestinal transit time, and constipation. They have generally been used in mild to moderate pain situations where the patient is able to tolerate oral medications. Ketorolac tromethamine is an NSAID that can be given parenterally, thereby circumventing the need for the patient to be able to tolerate enteral formulations, an issue immediately after intestinal surgery. Ketorolac inhibits the synthesis of prostaglandins through the inhibition of the cyclo-oxygenase enzyme system. At analgesic doses it has minimal anti-inflammatory and antipyretic activity. Ketorolac has been shown to have considerable analgesic properties without any deleterious effect on intestinal function [11]. It has in fact been shown, in randomized prospective trials to have an equivalent analgesic effect to morphine following major abdominal surgery, including colon resection [4, 5, 7, 20, 24].

This trial was designed to determine if addition of an NSAID in the form of ketorolac could minimize opioid requirements in patients not receiving epidural analgesia, resulting in decreased ileus and ultimately decreased length of hospital stay.

Methods

This trial protocol was approved by the hospital Research Ethics Board.

Population

This study was designed to be generalizable to all patients suitable to undergo laparoscopic colon resection that have no contraindication to NSAIDs or morphine. The study sample was drawn from all patients referred during the study period to the Centre for Minimally Invasive Surgery at St. Michael's Hospital in Toronto, Canada. Patients who met inclusion and exclusion criteria (Table 1) were prepared for trial entry and consent was obtained. Exclusion criteria consisted of additional factors deemed likely to influence hospital discharge.

Intervention

Patients were familiarized with the use of the PCA pump, the expected nature of their postoperative course, and the planned postoperative assessments. Patients were anaesthetized with standard general anesthesia using Propofol or pentothal with a benzodiazepine for induction of anesthesia. Inhalational anesthetic supplemented with intravenous propofol infusion was given for maintenance of general anesthesia. Short-acting opioids were permitted on induction and intraoperatively and as was up to 20 mg morphine depending on duration of surgery and clinical response. Nonsteroidal anti-inflammatory drugs were not permitted intraoperatively except for the study agent that was given at the end of surgery. All wounds were infiltrated by the surgeon with 0.25% marcaine with epinephrine prior to incision and again at closure.

Randomization was not performed until the operating surgeon confirmed that the procedure would be completed laparoscopically. Patients undergoing successful segmental laparoscopic colon resection were randomized with stratification according to (1) right or left colon lesion and (2) benign or malignant disease. Randomization was performed centrally by the research pharmacy according to a computer-generated randomization list, provided to the pharmacist by our statistician. All patients, care givers, and study personnel were blinded to study group. The study arm received ketorolac 30 mg given intravenously every 6 h for 48 h. The control arm received normal saline placebo intravenously on the same schedule. Study drugs were prepared by the pharmacy in identical bags. The first dose was given in the operating room prior to transfer to the Post Anesthetic Care Unit (PACU).

In the PACU, patients received morphine at the discretion of the consulting pain service. All patients received PCA morphine (1 mg bolus, lockout 5 min, 4-h limit 30 mg) on departure from the unit. Patient controlled analgesia was cared for by the pain service and discontinued on the third postoperative day if the patient was tolerating liquids, had used less than 30 mg morphine in the last 12 h, and had a pain score of less than 4/10. At this time oral naproxen was prescribed for

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Elective laparoscopic segmental colon resection	Emergency operation
Informed consent	Conversion to open surgery
	Stoma creation
Age > 16	Allergy to ketorolac or morphine
	Contraindication to NSAID (peptic ulcer disease,[a] renal insufficiency,[b] bleeding disorders)
	ASA class > III
	Planned ICU admission
	Therapeutic anticoagulation
	Social circumstances interfering with discharge planning
	Inability to tolerate/understand PCA
	Inflammatory bowel disease

[a] History of past ulcer disease with or without medical advice to avoid NSAIDs was accepted without confirmation of method of diagnosis
[b] Serum creatinine > 120 μmol/l
ASA, American Society of Anesthesiologists; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory medication; PCA, patient-controlled analgesia

all patients at 500 mg BID with supplemental oral acetaminophen 1,000 mg every 6 h. All patients were ambulated on the day following surgery.

Surgical technique: laparoscopic segmental colectomy

The technique of surgery varied depending on the procedure performed but was consistent between surgeons. All patients received a mechanical bowel preparation, parenteral antibiotics, and venous thrombosis prophlaxis preoperatively. Three surgeons experienced in laparoscopic colon surgery (> 100 cases each) performed all procedures. For right-side resections, after lateral to medial mobilization of the bowel laparoscopically, division of blood vessels, bowel resection, and anastomosis were performed extracorporeally through a small extension of the midline trocar incision.

For left-side resections, bowel mobilization, distal resection, and division of the blood supply were performed laparoscopically. Specimen extraction, proximal resection, and insertion of the endoluminal circular stapling anvil was through a small muscle-splitting incision in the left iliac fossa. A standard double-stapled anastomosis was completed under laparoscopic visualization. The splenic flexure was mobilized as necessary to ensure a tension-free anastomosis.

Foley catheters were removed on POD 1 unless otherwise indicated by the operating surgeon. Nasogastric tubes or drains were not used routinely. Dimenhydrinate was administered for nausea or vomiting unless evaluation indicated severe abdominal distension necessitating placement of a nasogastric tube.

Evaluation

Each patient was evaluated daily by a blinded research fellow and/or research coordinator. This evaluation included routine postoperative assessment (vitals, fluid status, etc.) in addition to postoperative data collection and administration of the visual analog scale (VAS) pain assessment (Table 2).

Diet advancement followed the guidelines set out in Table 3. Patients were discharged according to strict criteria. They must have been afebrile and have no postoperative complications, tolerating a full diet, passing flatus, and ambulatory. Pain must have been controlled by oral analgesics.

Sample size calculation

At the time of initiation of this study, 491 patients that would be considered eligible had already undergone successful laparoscopic colon resections by the St. Michael's Hospital Minimally Invasive Surgery group. The median length of hospital stay in this group was 5 days. It was considered clinically significant if hospital stay could be reduced by one full day through the use of ketorolac.

Based on this previous experience, the mean logarithmic transformed length of hospital stay has been 1.67 ± 0.54 (approx. 5.3 ± 1.7 days). Assuming similar outcomes in the control group and anticipating a reduction in postoperative hospital stay to approximately 4 days ($\log(4) = 1.39$) in the study group, then with 80% power to detect a difference and a 5% level of significance, 60 patients would need to be enrolled in each group.

For the primary outcome, statistical analysis consisted of Student's *t*-test of logarithmic transformed length of hospital stay. For secondary outcomes, the Student *t*-test, rank-sum test, chi-squared test, and Fisher's exact test were used where appropriate. For all comparisons, a p value of 0.05 was considered statistically significant.

Results

This study began recruitment in October 2002. The study was twice interrupted by the SARS epidemic in Toronto, and by March 2005 the study was closed when all three contributing surgeons had either departed the hospital (including the principle investigator) or had announced imminent plans to do so. During this period 190 patients were offered a laparoscopic colon resection and evaluated for trial entry. Of these, 94 were considered eligible and 80 (85%) consented to the study. Ten patients were found to be ineligible after consent and were withdrawn. Twenty were excluded prior to randomization comprising 11 conversions (16%), 7 requiring stoma formation, and two patients given ketorolac by the anesthetist at the start of anesthesia in violation of the protocol. Six patients were withdrawn after randomization (2 did not receive study medication on surgical ward, 1 converted after randomization, 1 unexpected admission to ICU after randomization, 2 withdrew themselves after randomization – one for perceived hypersensitivity to the administered analgesia without unblinding), leaving 22 patients in each group to complete the study (Fig. 1).

There we no differences between groups in sex distribution, age, weight, or body mass index or operation time (Table 4). No patient in either group met the discharge criteria prior to day 3. On day 3, five patients in the ketorolac group were discharged and none in the open group (Fig. 2). This was a significant difference in number of hospital inpatients for day 3 ($p = 0.024$, Fisher exact test). The ketorolac group maintained this lead until day 6, at which point eight total patients remained in hospital.

Two patients in the ketorolac group suffered anastomotic leaks in the early postoperative period and were excluded from further analysis because their care deviated significantly from the study protocol. The first leak was in a 37-year-old male 4 days post sigmoid colectomy for diverticulitis presenting with peritonitis. Computed tomography confirmed anastomotic leakage and the patient underwent reoperation for defunctioning. Discharge was in an additional 11 days. The second leak was a 60-year-old male 3 days post extended right colectomy for a transverse colon cancer presenting with localized abdominal pain, fever, and leukocytosis.

Table 2. Visual analog scale data sheet

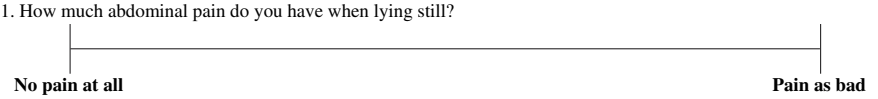
ORAL-CS PAIN ASSESSMENT

Date: _____ (DD-MM-YY) Time: _____

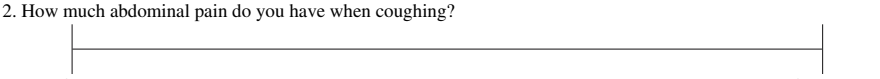
Post-op Day (circle): 1 2 3 4 5 6 7 ___ Hours Post-op: _____

For the following questions, draw a vertical mark on the line:

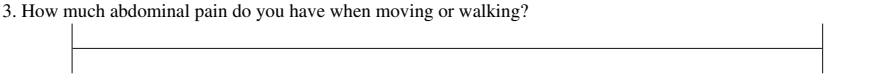
1. How much abdominal pain do you have when lying still?



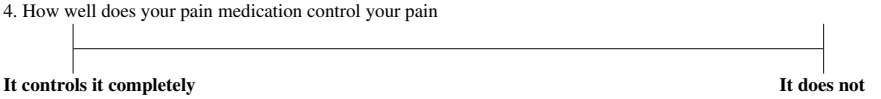
2. How much abdominal pain do you have when coughing?



3. How much abdominal pain do you have when moving or walking?



4. How well does your pain medication control your pain



5. How satisfied are you with the control of your pain?

1 **2** **3** **4** **5**

Not satisfied Very satisfied

Table 3. ORAL-CS diet advancement

Postoperative diet
- Stage 1: NPO
- Stage 2: Clear liquids
- Stage 3: Regular diet

Diet advancement criteria:

Diet may be advanced on the morning of each postoperative day until regular diet is reached if the following criteria are met:
1. No nausea or vomiting
2. No abdominal distension
3. Patient tolerated diet on previous day

All patients are stage 1 immediately following surgery.

All criteria must be met for diet advancement. If all criteria are not met, then a physician will determine appropriate management:
- Mild nausea, mild abdominal distension, or inability to tolerate diet:
  - Remain at same stage
- Moderate nausea, moderate abdominal distension, and/or one episode of emesis:
  - Revert back one stage
- Severe nausea, severe abdominal distension, and/or more than one episode of emesis:
  - NPO and nasogastric tube

NPO, nothing by mouth

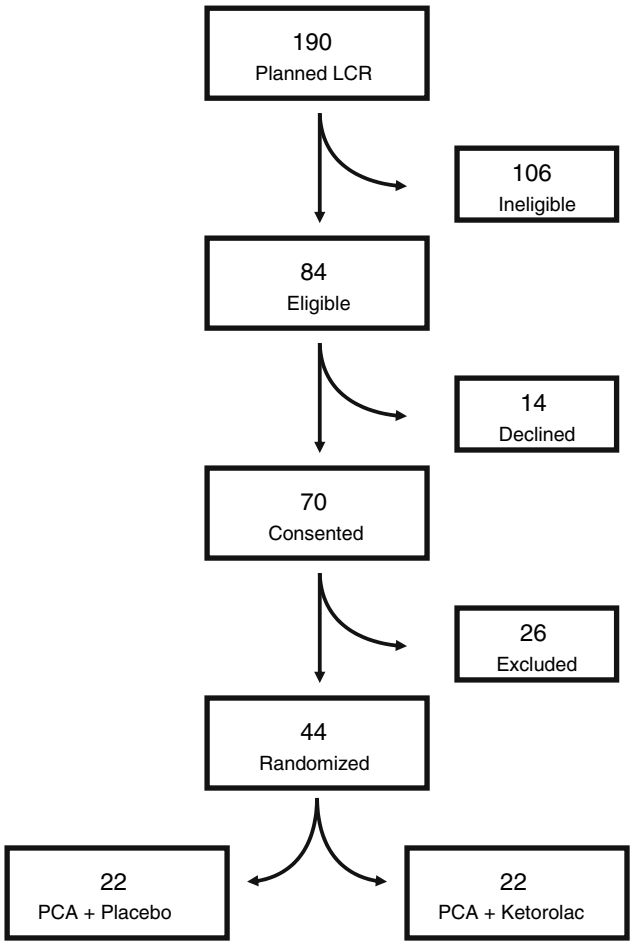


Fig. 1. Flowsheet of study recruitment. Of 190 patients evaluated, 44 were randomized.

Computed tomography confirmed a localized leak and the patient was treated with bowel rest and antibiotics. Discharge was in an additional 9 days.

Median length of stay for the entire study was 4.0 days, with significant correlation between milligrams of morphine consumed and time to first flatus ($r = 0.422$, $p = 0.005$), full diet ($r = 0.522$, $p < 0.001$), and discharge ($r = 0.437$, $p = 0.004$). Patients in the ketorolac group consumed less morphine and had less time to first flatus and full diet. The reduction in length of stay was not significant (Table 5).

Pain control appeared superior in the ketorolac group. Patients in the ketorolac group reported less pain walking (Fig. 5) and better overall pain control (Fig. 6) than placebo controls on days one through three. Ketorolac patients also reported greater satisfaction with pain control in the first 48 hours (Fig. 7). Ketorolac patients staying 4 days reported greater pain coughing than placebo patients (Fig. 4).

Three patients required readmission for anastomotic leakage. In the ketorolac group, a 50-year-old male discharged 4 days post right colectomy for a polyp and a 68-year-old female discharged 3 days post right colectomy for cancer both returned in five days with pain, fever, and leukocytosis. Computed tomography confirmed localized leaks, and both patients were treated in hospital with bowel rest and antibiotics for an additional 4 and 8 days, respectively. In the placebo group an 82-year-old female discharged 4 days post sigmoid colectomy for cancer was readmitted 3 days later with peritonitis and defunctioned. She was discharged in an additional 24 days. In total, five anastomotic leaks were recorded (4 in the ketorolac group versus 1 in the placebo group, $p = 0.15$), two of which required reoperation. Leaks were not associated with operating surgeon.

Additional complications that occurred included one deep vein thrombosis (requiring readmission), one pneumonia, one supraventricular tachycardia, and one patient that returned to emergency with throat swelling and shortness of breath but was not readmitted. There were no deaths.

Discussion

The exact etiology of postoperative ileus is unclear, but it is generally believed to be secondary to inhibition of intestinal motility due to a sympathetic reflex caused by operative trauma [10, 13]. Reducing operative trauma should decrease ileus. This has been shown in several studies of laparoscopic versus open colectomy [3, 8]. However, ileus and therefore delayed recovery of intestinal function has also been attributed to opioid usage [6, 16]. Therefore any reduction of opioid usage should also have a beneficial effect on duration of postoperative ileus. Laparoscopic surgery has been shown to lead to decreased opioid use as a result of the overall decreased pain associated with this operative approach [23]. However, opioid-based regimens still form the basis for postoperative pain management in colon resection in most centers.

Kehlet and Wilmore have demonstrated impressively short length of hospital stay with a multimodal approach to open and laparoscopic colon surgery [17]. They have even provided some evidence that the ileus-reducing advantages of laparoscopy may be negligible if an aggressive multimodal approach is taken with open colon surgery [2, 17]. However, their study did suffer concerns of high readmission rate and mortality in the open surgery group.

The present study was a very simple design to measure the isolated effect of supplementing (or possibly replacing) PCA morphine with an NSAID, specifically ketorolac. This study encountered a number of challenges that impaired its progress: it was twice interrupted by the SARS epidemic in Toronto, which slowed accrual; in addition, when we became concerned about higher than usual leak rate in the study, the trial was voluntarily suspended after 40 patients while an ad hoc independent safety review committee evaluated the results to that point. Nineteen prospective patients were lost during this period alone. The committee allowed the trial to continue but showed enough concern to request a second review at 60 cases. That goal was never reached, as all surgeons participating in this single-center study left the institution.

In designing this trial it was estimated that greater than 80% of referrals would meet the inclusion criteria,

Table 4. Group comparison

	Placebo	Ketorolac	*P* Value
Number of patients	22	22	
Age (years)	61.4 ± 12.4	59.5 ± 8.2	0.574
Sex (male/female)	8/14	12/10	0.364
Weight (kg)	79.4 ± 17.0	77.5 ± 13.0	0.689
BMI (kg/m^2)	27.3 ± 4.9	27.1 ± 3.2	0.883
Stratification			
Benign/malignant	10/12	12/10	0.763
Left/right	14/8	12/10	0.364
Operating time (min)	195 ± 70	177 ± 39	0.328

BMI, body mass index

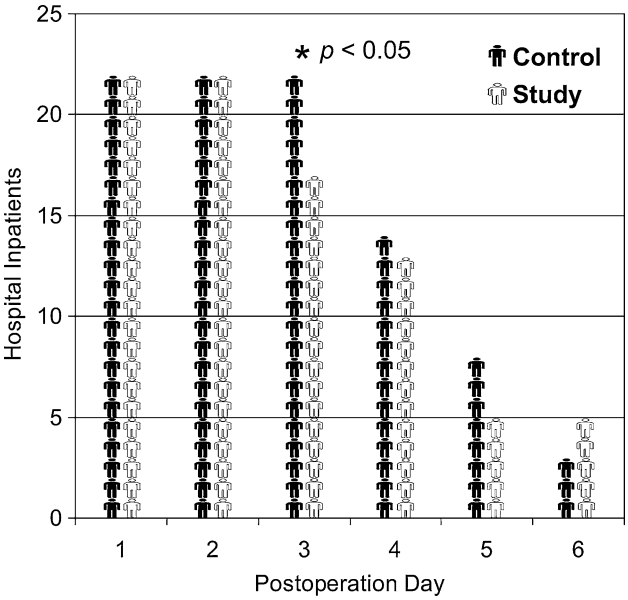


Fig. 2. Hospital inpatients by day. On day 3 there were significantly fewer inpatients in the ketorolac group.

Table 5. Study outcomes

	Placebo	Ketorolac	*p* Value
Number of patients	22	22	
Morphine required (mg)	63 ± 41	33 ± 31	0.011
Median first flatus (days)	3.0 days	2.0 days	< 0.001
Median full diet (days)	3.0 days	2.5 days	0.033
Length of stay (days)			
Median	4.0 days	4.0 days	0.142
Mean	4.5 days	3.6 days	
Logarithmic transformed mean	1.43 ± 0.37	1.22 ± 0.39	0.082

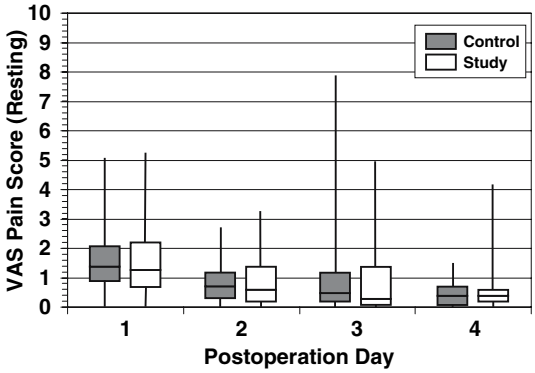


Fig. 3. Box and whisker plot of pain at rest by hospital day as measured by visual analog scale (VAS). There were no differences between groups.

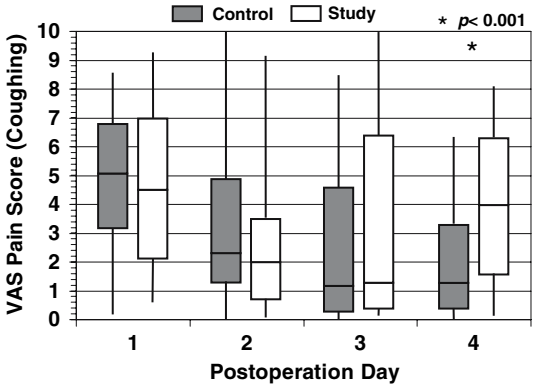


Fig. 4. Box and whisker plot of pain coughing by hospital day as measured by visual analog scale (VAS). The ketorolac group reported greater pain at day 4.

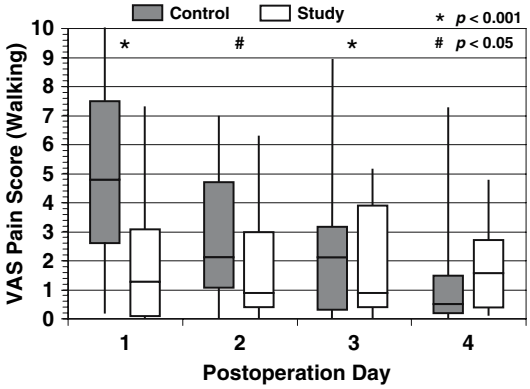


Fig. 5. Box and whisker plot of pain walking by hospital day as measured by visual analog scale (VAS). The ketorolac group had significantly less pain in the first 3 days.

yet only 44% met the criteria in reality. Most of the exclusions were to prevent confounding by factors that might delay discharge (ICU stay, stoma teaching, social circumstances) but did not represent a contraindication to NSAID. Only 17% of our study population had such a contraindication. Fifteen of these gave a prior history of peptic ulcer disease. We accepted this diagnosis without confirmation by endoscopy or barium swallow.

The findings of reduced ileus in this study as measured by passage of first flatus and time to full diet are consistent with previous reports in colon surgery cited above. The overall median length of hospital stay was only 4 days, less than most major randomized trials [9, 12, 14, 18, 25], and there were significantly fewer inpatients on day 3 in the ketorolac group. This advantage

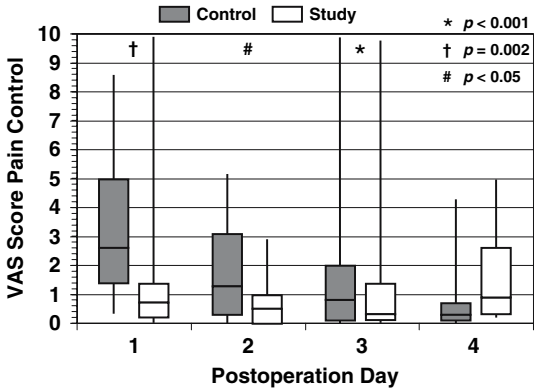


Fig. 6. Box and whisker plot of pain control as measured by visual analog scale (VAS).

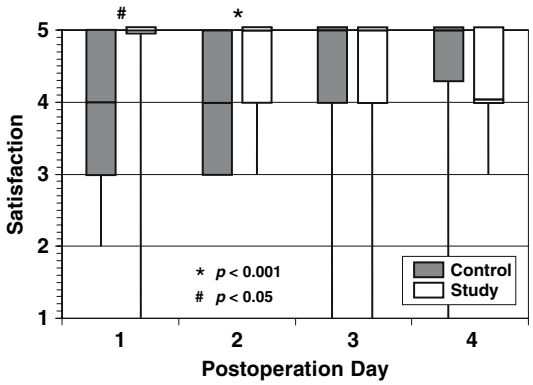


Fig. 7. Box and whisker plot of satisfaction with pain control as measured by Likert scale. The ketorolac group were more satisfied in the first 2 days.

was lost in subsequent days, and overall reduction in length of hospital stay was not significant. We suggest that this was most likely due to early trial termination and unfortunate underpowering of the analysis. One can only wonder what outcome could have been achieved with 120 patients, as originally planned.

Superior pain control (walking and satisfaction) were noted over the first 3 days in the ketorolac group, a finding that has been observed before [20]. Why the placebo group should report better pain control (coughing) at day 4 is not clear, except to recognize that only 50% of the ketorolac group remained in hospital by day 4 and may represent the patients with more significant recovery issues.

The incidence of anastomotic leaks in this study is concerning. The overall leak rate was 11% (18% in the ketorolac group). This is much higher than the authors' previously reported experience. In an antecedent series of 750 laparoscopic colon resections by the same surgeons, the leak rate was 2.5%, well within accepted limits [21]. We suggest it is therefore unlikely that this finding arose as a result of inadequate surgical technique. Four of these leaks were in the ketorolac group, yet there is no evidence in other colon studies to suggest that ketorolac impairs wound healing or increases anastomotic leak rates. It is therefore also unlikely that this finding has uncovered a previously unappreciated effect of ketorolac on anastomosis healing. The leaks make the data difficult to interpret. We suggest that this outcome may simply represent an early cluster of leaks in an unfortunately underpowered study. The evaluation of the efficacy of this protocol may be justified by excluding these complications as anomalies.

Conclusions

This prospective, double-blind, placebo-controlled, randomized clinical trial comparing intravenous ketorolac to placebo for postoperative pain control in patients undergoing laparoscopic segmental colon resections with supplemental PCA morphine analgesia demonstrated that ketorolac reduces postoperative ileus and morphine requirements. The primary outcome of a reduction in length of hospital stay was not appreciated, likely because of underpowering from early trial termination. Anastomotic leak rates were higher than usual, with most occurring in the ketorolac group, but with no precedent for this in other studies we can only suggest this was an anomaly. The evidence presented here suggests that in patients with no contraindication to NSAIDs, ketorolac should be a routine part of the postoperative pain management regimen for laparoscopic colon surgery.

Acknowledgments. The authors are grateful to the following clinical fellows in advanced minimally invasive surgery at St. Michael's Hospital who contributed to this study: Drs. Eric Bédard, Yves Bendavid, Robin Boushey, Laz Klein, Deepa Kumar, and Keneth Pace.This study was funded by a research grant from the Physicians' Services Incorporated Foundation

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