Int J Colorectal Dis (2008) 23:1175–1183
DOI 10.1007/s00384-008-0536-7

ORIGINAL ARTICLE

Effect of bisacodyl on postoperative bowel motility in elective colorectal surgery: a prospective, randomized trial

U. Zingg · D. Miskovic · I. Pasternak · P. Meyer · C. T. Hamel · U. Metzger

Accepted: 26 June 2008 / Published online: 30 July 2008

Abstract
Background Postoperative ileus is a common condition after abdominal surgery. Many prokinetic drugs have been evaluated including osmotic laxatives. The data on colon-stimulating laxatives are scarce. This prospective, randomized, double-blind trial investigates the effect of the colon-stimulating laxative bisacodyl on postoperative ileus in elective colorectal resections.
Materials and methods Between November 2004 and February 2007, 200 consecutive patients were randomly assigned to receive either bisacodyl or placebo. Primary endpoint was time to gastrointestinal recovery (mean time to first flatus passed, first defecation, and first solid food tolerated; GI-3). Secondary endpoints were incidence and duration of nasogastric tube reinsertion, incidence of vomiting, length of hospital stay, and visual analogue scores for pain, cramps, and nausea.
Results One hundred sixty-nine patients were analyzed, and 31 patients discontinued the study. Groups were comparable in baseline demographics. Time to GI-3 was significantly shorter in the bisacodyl group (3.0 versus 3.7 days, P=0.007). Of the single parameters defining GI-3, there was a 1-day difference in time to defecation in favor to the bisacodyl group (3.0 versus 4.0 days, P=0.001), whereas no significant difference in time to first flatus or tolerance of solid food was seen. No significant difference in the secondary endpoints was seen. Morbidity and mortality did not differ between groups.
Conclusion Bisacodyl accelerated gastrointestinal recovery and might be considered as part of multimodal recovery programs after colorectal surgery.

Keywords Bisacodyl · Colorectal resection · Gastrointestinal recovery · Postoperative ileus · Colon-stimulating laxatives

U. Zingg · D. Miskovic · I. Pasternak · P. Meyer · U. Metzger
Department of Surgery, Triemli Hospital,
Birmensdorferstr. 497,
8063 Zurich, Switzerland

U. Zingg (✉) · C. T. Hamel
Department of Surgery, University Hospital of Basel,
Spitalstrasse 21,
4031 Basel, Switzerland
e-mail: uzingg@uhbs.ch

Introduction

Postoperative ileus, characterized by nausea, vomiting, abdominal distension, and pain, occurs frequently following abdominal surgery. It leads to patient discomfort, may contribute to related complications and consequently to a prolonged length of hospital stay. Multiple factors, including surgical manipulation, inflammatory mediators, autonomic dysfunction, electrolyte and fluid imbalances, and analgesics (opioids) contribute to the etiology [1, 2].

Without specific treatment, postoperative ileus resolves spontaneously within 4 to 5 days. Whereas small bowel and stomach recover early, colonic motility is the last to return [3–5]. Current treatment approaches involve minimally invasive surgery and different multimodal rehabilitation programs (fast track), including epidural analgesia, enforced mobilization, early feeding, immediate removal of catheters, curved or transverse incisions, and a variety of prokinetic agents [6–10].

Several pharmacologic studies have been carried out to evaluate the effect of different agents, such as metoclopramide, erythromycin, tropisetron, alvimopan, neostigmine, and cisapride on postoperative ileus [11–22]. Only cisapride, which has been removed from the market for cardiac side

effects, and alvimopan showed a significant acceleration of gastrointestinal recovery [15, 16, 22].

Although there is evidence that the normalization of colonic motility is the most decisive factor for full recovery of gastrointestinal function, there are only two studies evaluating the role of colon-stimulating laxatives on the recovery of postoperative gastrointestinal function [23, 24]. The first is a prospective observational study and the second is a randomized trial with 23 patients in each arm. Both studies indicated an earlier return of bowel movement.

Bisacodyl is a laxative of the triarylmethane group, which is hydrolyzed in the bowel by local enzymes into the active agent bis-(*p*-hydroxyphenyl)-pyridyl-2-methane (BHPM). BHPM directly stimulates colonic peristalsis.

The aim of this randomized, double-blind, placebo-controlled trial was to investigate the effect of bisacodyl on the duration of postoperative ileus in patients undergoing elective colorectal resection.

Materials and methods

All adult patients (>18 years, <90 years) admitted for elective open or laparoscopic colorectal resection at the Triemli Hospital in Zurich, Switzerland, were evaluated for eligibility. Exclusion criteria were: preoperatively planned protective ileostomy or definite colostomy, emergency surgery, pregnancy, and known hypersensitivity for bisacodyl.

The trial was registered by the National Library of Medicine at www.clinicaltrials.gov under the number NCT00509327. The study was approved by the local ethics committee and the Swiss Federal Agency for Therapeutic Products (Swissmedic). Written informed consent was obtained from each patient before enrolment in the study.

Study design

Patients were randomized using a computer system to receive either 10 mg bisacodyl (Dulcolax®, Boehringer Ingelheim, Switzerland) in an opaque capsule orally or identical placebo capsules (glucosemonohydricum). Manufacturing of the capsules was done by the hospital pharmacy. The capsules were administered twice daily, beginning 1 day prior to surgery and ending on postoperative day 3. Rationale for length of bisacodyl administration was the fact that postoperative ileus has been shown to resolve spontaneously by days 4 to 5. Patients and all involved medical personnel were blinded.

Bowel preparation was not prescribed for open surgery, whereas in patients undergoing laparoscopic resection, 2 l of sodium sulfate/macrogol solution (Cololyt®, Spirig Pharma AG, Switzerland) was administered. Thoracic epidural analgesia was discussed with every patient. In the absence of contraindications (previous back surgery, severe spondylarthrosis, coagulopathy) and with agreement of the patient, an epidural catheter was placed between Th 8 and Th 12 at induction of anesthesia. Postoperatively, the thoracic epidural catheter was left in situ and a solution consisting of 48 ml 0.125% bupivacaine (Duracain®, Sintetica, Mendrisio, Switzerland) with 2 ml fentanyl (Fentanyl-Curamed®, Opopharma, Zurich, Switzerland) was administered for continuous analgesia during the first five postoperative days.

Standard colorectal surgery was performed in all patients. We performed a midline incision for open surgery and a four-port technique with removal of the specimen through a small transverse incision in the lower abdomen for laparoscopic procedures. All patients received perioperative single shot antibiotics (cefuroxime 1.5 g and metronidazole 1 g i.v.). The nasogastric tube (NGT) was removed at the end of the operation.

All patients received a basic analgesia of 0.5 to 1 g paracetamol (Dafalgan®, Bristol-Myers Squibb, Baar, Switzerland) given orally every 6 h. For additional pain relief, metamizol (Novalgin®, Sanofi-Aventis, Meyrin, Switzerland) was used as first line reserve and morphine or its derivates as second line reserve. Opioid consumption was monitored during the first eight postoperative days. To allow comparison between groups concerning consumption, all opioids were converted to an equivalent morphine dose.

Nutrition was started on the first postoperative day. We used a five-step diet protocol, starting with limited fluids (1,000 ml/day), followed by free fluids, soft food, light meals, and normal diet. The next step was given if patients had bowel movement, no nausea, and tolerated the previously given nutrition.

Data analysis

The primary endpoint was recovery of gastrointestinal function, defined as the mean time to the occurrence of the following events (GI-3): first flatus passed, first defecation, and first solid food tolerated. We did not include the presence of bowel sounds, as these may occur due to small bowel activity and be present before colonic recovery [25]. Secondary endpoints were the incidence and duration of NGT reinsertion, incidence of postoperative vomiting, and length of hospital stay. Indication for NGT reinsertion was repetitive nausea or vomiting. Reinserted NGT was left in situ until secretion was less than 100 ml per 24 h. Additionally, consumption of analgesics was documented and scores for pain, cramps, and nausea, assessed by a standard visual analogue scale (VAS) during the first eight postoperative days, were monitored [26]. GI-3 and VAS scores were obtained daily by the responsible intern during the morning ward rounds. The VAS

consisted of a 10-cm ruler with a scale from 0 (no pain) to 10 (highest imaginable pain). Other variables recorded were patients' demographics, use of epidural anesthesia, type and duration of surgery, and morbidity.

Statistical analysis

A sample size of 80 patients in each group was calculated assuming that the time to full gastrointestinal recovery (GI-3) would be reached 20% earlier in the bisacodyl group (4 versus 5 days in the placebo group) with a significance of 5% and 90% power. To allow for dropouts, for example due to preoperatively unexpected need for stoma, it was planned to include a total number of 200 patients.

The groups were compared by means of the Mann–Whitney *U* test for continuous data and the Fisher's exact test for non-continuous data. In case of normal distribution, a Student's *t* test was applied. A two-tailed $P \leq 0.05$ was considered statistically significant. GraphPad InStat® version 3.06 (GraphPad Software Inc., San Diego, USA) was used for statistical calculations.

Results

Of the 283 patients assessed for eligibility between November 2004 and February 2007, 43 did not meet the inclusion criteria (preoperative planned protective stoma formation, extirpation of rectum with terminal stoma) and 40 refused to participate. Fourteen patients in the placebo group and 17 in the bisacodyl group discontinued the study (Fig. 1). The characteristics of the remaining 169 patients are shown in Table 1. With the exception of a significant difference in the surgery duration, groups were comparable in baseline demographics and perioperative data. Rectosigmoid resection (n=103, 60.9%) was most often performed, followed by right hemicolectomy (n=31, 18.3%). Colon or rectal cancer was the primary indication in almost half of patients (n=79, 46.7%). Diverticular disease accounted for 42.0% of surgical procedures (n=71).

Time to gastrointestinal recovery (GI-3) was significantly shorter in the bisacodyl group (median 3.0 days [1–12.3]; mean 3.4 days [±1.7] versus median 3.7 days [1.7–10.7]; mean 4.0 days [±1.6], P=0.007). Of the single parameters

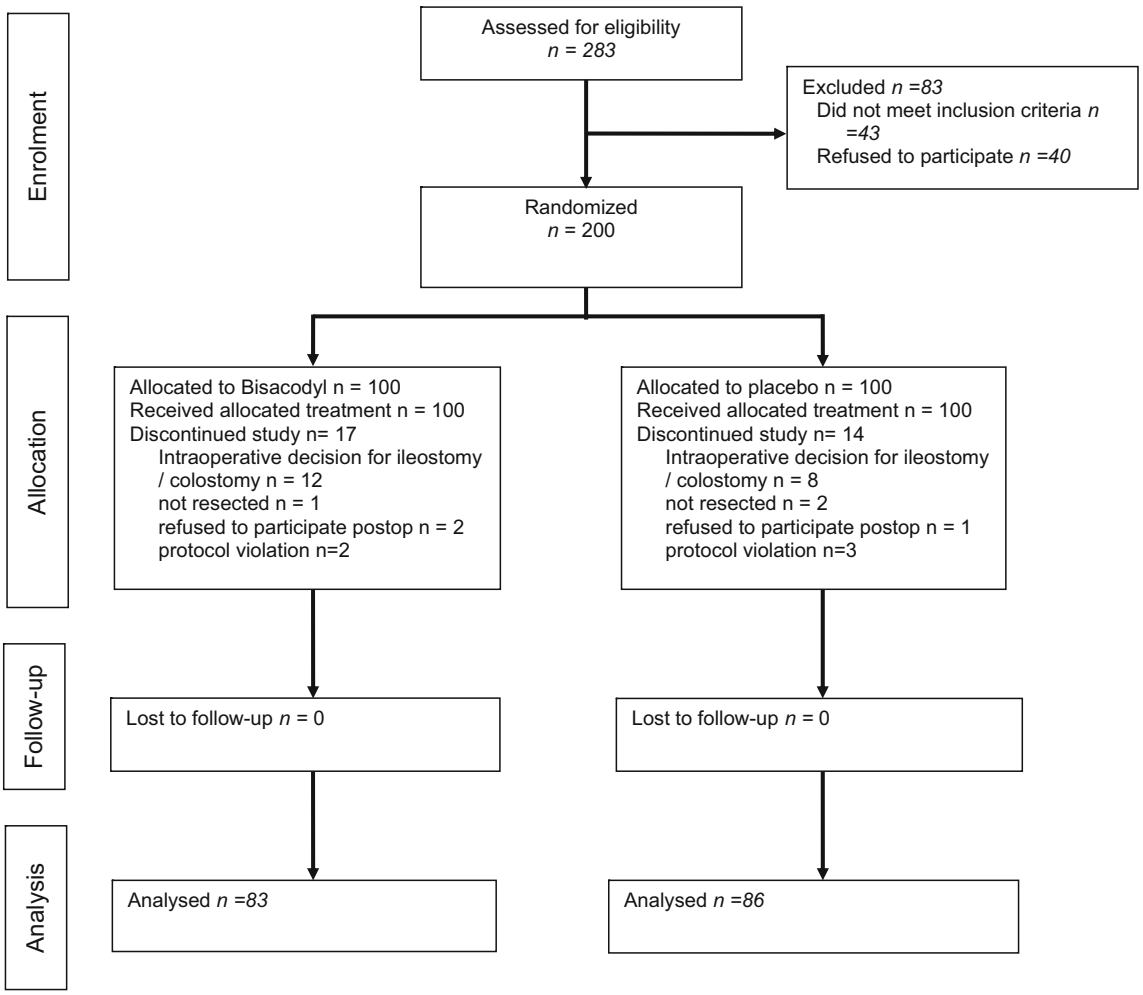

Fig. 1 Trial profile

Table 1 Patient characteristics and baseline data

	Bisacodyl (n=83)	Placebo (n=86)	P value
Mean (SD) age (years)	67.9 (±13.2)	66.4 (±14.5)	0.484
Males (%)	42 (50.6)	54 (62.8)	0.122
Comorbidities			
COPD (%)	8 (9.6)	10 (11.6)	0.804
Diabetes mellitus (%)	8 (9.6)	10 (11.6)	0.804
Cardiac (%)	7 (8.4)	4 (4.7)	0.365
Diagnosis			
Cancer (%)	40 (48.2)	39 (45.4)	0.759
Diverticulosis (%)	34 (41)	37 (43)	0.757
Other (%)	9 (10.8)	10 (11.6)	1.000
Type of surgery			
Right hemicolectomy (%)	16 (19.3)	15 (17.4)	0.843
Left hemicolectomy (%)	6 (7.2)	4 (4.7)	0.530
Rectosigmoid resection (%)	49 (59)	54 (62.8)	0.639
Anterior resection (%)	11 (13.3)	7 (8.1)	0.325
Subtotal colectomy (%)	0	1 (1.2)	1.000
Ileocecal resection (%)	1 (1.2)	3 (3.5)	0.621
Segmental resection (%)	0	2 (2.3)	0.497
Mean (SD) duration of surgery (min)	157 (±44.2)	172 (±52.3)	0.046
Open surgery (%)	47 (56.6)	47 (54.6)	0.877
Laparoscopic surgery (%)	29 (34.9)	31 (36.1)	1.000
Conversion (%)	7 (8.4)	8 (9.3)	1.000
Epidural analgesia (%)	51 (61.5)	50 (58.1)	0.754
Median (range) cumulative morphine consumption first 8 days (mg)	12 (0–467)	22.5 (0–486)	0.092
Mean (SD) cumulative morphine consumption first 8 days (mg)	40.2 (±72.3)	59.4 (±90.9)	
Mechanical bowel preparation (%)	31 (37.4)	33 (38.4)	1.000

COPD Chronic obstructive lung disease

defining the GI-3, there was a significant difference in time to defecation in favor to the bisacodyl group (median 3.0 days [1–8]; mean 3.1 days [±1.9] versus median 4.0 days [1–8]; mean 4.2 days [±2.1], P=0.001), whereas no significant difference in time to first flatus or tolerance of solid food was seen (Table 2). We did not observe any significant between-group differences among the secondary endpoints (Table 3). Reinsertion of NGT was necessary in 11 (13.3%) patients treated with bisacodyl compared to 13 (15.1%) with placebo. There was a tendency for longer duration of NGT reinsertion in the bisacodyl group (2.8 [±1.3] days versus 1.8 [±0.9] days, P=0.055). In this subgroup of patients with NGT reinsertion, no significant differences in baseline characteristics were seen (Table 4).

We distinguished surgical and non-surgical morbidity, including minor complications such as superficial surgical site infections and urinary tract infections (Table 5). No significant difference between groups was noted. Overall surgical morbidity was 23.1%, whereas non-surgical complications occurred in 13% of all patients.

There was no difference in opioid consumption during the first eight postoperative days between groups (bisa-

Table 2 Effect of bisacodyl on gastrointestinal recovery

	Bisacodyl (n=83)		Placebo (n=86)		P value
	Median (range)	Mean (SD)	Median (range)	Mean (SD)	
GI-3 (days)	3.0 (0.7–12.3)	3.4 (±1.7)	3.7 (1.7–10.7)	4.0 (±1.6)	0.007
First defecation (days)	3.0 (1–8)	3.1 (±1.9)	4.0 (1–8)	4.3 (±2.1)	0.001
First flatus (days)	2.0 (1–7)	1.9 (±1.1)	2.0 (1–7)	2.3 (±1.4)	0.126
First solid food (days)	4.0 (2–30)	5.3 (±3.6)	4.0 (2–23)	5.4 (±3.3)	0.921

GI-3 defined as mean time to occurrence of all three of the following events: first flatus passed, first defecation, and solid food tolerated.

Table 3 Incidence and duration of NGT reinsertion, postoperative vomiting, and length of hospital stay

	Bisacodyl (n=83)	Placebo (n=86)	P value
Incidence of NGT reinsertion (%)	11 (13.3)	13 (15.1)	0.827
Mean (SD) duration of NGT reinsertion (days)	2.8 (±1.3)	1.8 (±0.9)	0.055
Incidence of postoperative vomiting (%)	19 (22.9)	22 (25.6)	0.722
Median (range) length of hospital stay (days)	13 (4–92)	13 (6–74)	0.768
Mean (±SD) length of hospital stay (days)	16 (±12)	15 (±19)	

codyl: median 12 mg [0–467], mean 40 mg [±72]; placebo: median 22.5 mg [0–486], mean 59 mg [±91]; P=0.092). Pain, nausea, and cramping VAS results did not significantly differ between groups (Fig. 2a–c). Oral administration of bisacodyl was not associated with any side effects.

Discussion

In this study, pre- and postoperative administration of bisacodyl resulted in acceleration of overall gastrointestinal recovery (GI-3). Defecation occurred significantly earlier in the bisacodyl group, indicating a direct beneficial effect on postoperative colonic hypomotility. However, other clinically relevant factors such as time to tolerance of food or length of hospital stay did not significantly differ. Preoperative stimulation with bisacodyl may maintain the mobility of the colon throughout the surgical procedure, thus limiting the negative effect of surgery. During recovery from postoperative ileus, the most significant factor is colonic motility so that direct pharmacologic stimulation may play an important role [1, 4, 25, 27]. Huge et al. were able to demonstrate a decrease of colonic tone in patients undergoing left colonic surgery on the second and third postoperative days and a severely impaired colonic motility after surgery [25]. Steadman et al. found a relaxation of the descending colon in fasting subjects after administration of morphine intravenously [28]. These findings substantiate the importance of colonic stimulation postoperatively, as many patients will require analgesia with morphine or its derivates.

Table 4 Basic characteristics of the subgroup of patients with NGT reinsertion

	Bisacodyl (n=11)	Placebo (n=13)	P value
Mean (SD) age (years)	70.5 (±11.5)	68.6 (±10.6)	0.434
Males (%)	9 (81.8)	8 (61.5)	0.122
Comorbidities			
COPD (%)	0	1 (7.7)	1.000
Diabetes mellitus (%)	1 (9.1)	4 (30.8)	0.327
Cardiac (%)	1 (9.1)	1 (7.7)	1.000
Diagnosis			0.386
Cancer (%)	9 (81.8)	8 (61.5)	
Diverticulosis (%)	2 (18.2)	5 (38.5)	
Type of surgery			0.390
Right hemicolectomy (%)	4 (36.4)	3 (23.1)	
Left hemicolectomy (%)	1 (9.1)	0	
Rectosigmoid resection (%)	4 (36.4)	8 (61.5)	
Anterior resection (%)	2 (18.2)	1 (7.7)	
Ileocecal resection (%)	0	1 (7.7)	
Mean (SD) duration of surgery (min)	154 (±31)	182 (±60)	0.186
Open surgery (%)	8 (72.7)	11 (84.6)	0.630
Conversion (%)	2 (18.2)	2 (15.4)	1.000
Epidural analgesia (%)	7	6	0.444
Median (range) cumulative morphine consumption first 8 days (mg)	8 (0–163)	64 (0–179)	0.068
Mean (SD) cumulative morphine consumption first 8 days (mg)	31.1 (±48.2)	70.7 (±61.8)	
Mechanical bowel preparation (%)	5 (45.5)	4 (30.8)	1.000

NGT Nasogastric tube

Table 5 Surgical and non-surgical morbidity

	Bisacodyl (n=83), n (%)	Placebo (n=86), n (%)	P value
Surgical morbidity			
Anastomotic leak	7 (8.4)	4 (4.7)	0.365
Deep surgical site infection	1 (1.2)	2 (2.3)	1.000
Superficial surgical site infection	4 (4.8)	3 (3.5)	0.717
Dehiscence of abdominal fascia	2 (2.4)	0	0.246
Postoperative bleeding	1 (1.2)	1 (1.2)	1.000
Non-surgical morbidity			
Pneumonia	5 (6)	1 (1.2)	0.113
Pulmonary embolism	1 (1.2)	0	0.491
Cardiac failure	1 (1.2)	1 (1.2)	1.000
Renal failure	1 (1.2)	1 (1.2)	1.000
Urinary tract infection	3 (3.6)	3 (3.5)	1.000

Morphine consumption during the first 8 days did not significantly differ. However, patients in the bisacodyl group had an average of 10 mg more morphine over the first 8 days, resulting in approximately 1 mg per day. This very low daily dose is unlikely to have an effect on gastrointestinal recovery, especially as the median effective analgesic dose of morphine has been described to be 5 mg [29]. Cali et al. showed a direct correlation between the amount of morphine and the return of gastrointestinal function in patients undergoing colectomy [30]. However, patients receiving under 25 mg total morphine were found to have approximately 25 h until normal bowel sounds were audible, 36 h until first flatus was reported, and 60 h until first bowel movement was reported. These times are comparable to the spontaneous resolution of postoperative ileus after 4–5 days [3–5]. Consequently, the difference of a total of 10 mg morphine in our study might not have influenced the gastrointestinal recovery time.

Concerning incidence and duration of NGT reinsertion, incidence of postoperative vomiting, and length of hospital stay, no difference between groups was noted. We found no satisfactory explanation for the tendency for longer NGT reinsertion in the bisacodyl group. The analysis of the patients with NGT reinsertion showed no significant differences between the bisacodyl and placebo collectives. Notably, the consumption of morphine tended to be higher in the placebo group. One reason for this finding might be the fact that three patients in the placebo subgroup suffered from complications with consecutively higher and longer need for opioids (abscess in splenic flexure, anastomotic leakage, postoperative mechanical ileus). However, the total number in this subgroup of patients is low, thus limiting the ability to draw definite conclusions.

The only significantly different intraoperative variable was duration of surgery. We were not able to explain the mean difference of 15 min between groups. Neither the type of surgery nor the level of training of the operating surgeon was different. Gervaz et al. reported of earlier return of gastrointestinal function if the procedure was performed by a specialist colorectal surgeon compared to general surgeons [31]. Unfortunately, there is no mentioning of duration of surgery in their study. However, the authors mention that more left-sided colectomies and more difficult cases were operated by the colorectal surgeon, thus implicating longer procedures. In other studies, no direct relationship between length of surgical procedure and duration of postoperative ileus could be demonstrated [32, 33]. We do not believe that the small difference of 15 min between the collectives had any impact on postoperative gastrointestinal recovery.

To our knowledge, only one randomized trial evaluated the effect of colon-stimulating laxatives (bisacodyl) on postoperative ileus [24]. These authors found a significant reduction of time to first bowel movement in 46 patients undergoing appendectomy. Fanning et al. investigated in a prospective observational study the effects of a combination of milk of magnesia and bisacodyl suppositories and reported an earlier return of bowel movements and shortened hospital stay [23]. However, these authors did not elaborate which of the agents showed a greater stimulatory effect.

In the present study, no difference in peri- or postoperative morbidity was noted. There was a slightly higher anastomotic leak rate in the bisacodyl group, however, far from significance. Bisacodyl had no side effects. The VAS for cramps, a known possible effect of bisacodyl, did not differ between groups. The analgesic requirements and VAS for pain were similar. There was no significant difference in the amount of opioids administered during the first 8 days between groups.

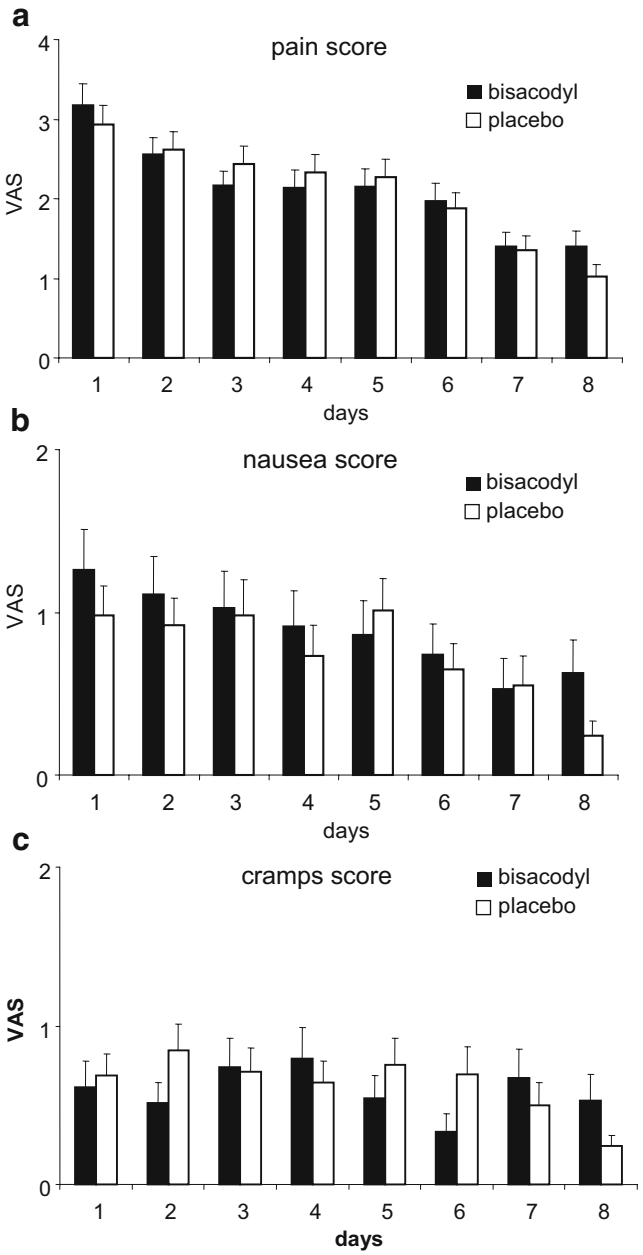

Fig. 2 VAS during the first eight postoperative days: **a** pain; **b** nausea; **c** cramping. All values are mean (SEM). No significant difference between the bisacodyl and placebo groups

Many pharmacologic agents have been evaluated for their effect on postoperative ileus. Apart from cisapride, which has been removed from the market, only alvimopan, a peripherally acting μ opioid antagonist, has shown an accelerated recovery time [15, 16, 21, 22]. Neither metoclopramide nor erythromycin altered the course of postoperative ileus although they may have a role in the treatment of nausea or impaired stomach emptying due to pyloric spasm [12, 13, 17, 18, 34, 35]. Other prokinetic drugs, such as neostigmine, propranolol, or tropisetron, had no proven effect on postoperative ileus [14, 20, 36, 37].

The pathogenesis of postoperative ileus is multifactorial. Autonomic dysfunction with increased influence of the sympathetic system resulting in inhibition of gut motility, inflammatory response due to surgical trauma, and administration of opioid drugs are important causes of postoperative gastrointestinal dysfunction [3, 38]. Gentle surgical technique and the use of minimal invasive techniques result in lower systemic cytokine levels reflecting a lower inflammatory reaction [39]. Additionally, laparoscopic surgery reduces postoperative pain, thus reducing autonomic sympathetic activity. In this study, the proportion of open and laparoscopic procedures was similar in both groups (bisacodyl: open surgery in 57%; placebo: 55%, P=0.877).

Epidural analgesia has been shown to decrease sympathetic response and opioid consumption and consequently postoperative ileus. Epidural analgesia carries a certain risk for adverse effects and is not feasible in all patients, for example those with spondylodesis or severe spondylarthrosis, but is currently considered as one of the most effective methods [1, 40]. The number of patients receiving a mid-thoracic epidural catheter was similar between the bisacodyl and placebo groups. At our institution, the placement of an epidural catheter was discussed with all patients undergoing colorectal resection, regardless of technique. We considered previous back surgery, coagulopathy, severe spondylarthrosis, and refusal by the patient as contraindications.

Most multimodal management protocols involve a wide range of other measures, such as enforced mobilization, avoidance of drains and NGT, early oral nutrition, and fluid restriction [10, 34, 35, 41, 42]. A minority of these fast-track protocols include the use of laxatives, mostly magnesia, an osmotic agent without colon-stimulating properties [7, 9, 43, 44]. The inclusion of a colon-stimulating laxative in rehabilitation programs may confer additional benefit by decreasing the duration of colonic hypomotility.

The study has some limitations. Patients were not stratified according to the method of surgery (laparoscopic or open resection). Furthermore, postoperative pain management with or without epidural analgesia was not standardized. However, the groups did not differ in these items.

In conclusion, the findings of this study suggest that pre- and postoperative administration of bisacodyl has a beneficial effect on gastrointestinal recovery after colorectal resection. Bisacodyl had no influence on time to tolerance of solid food or length of hospital stay. Colon-stimulating laxatives might be considered as part of multimodal recovery programs after colorectal surgery.

Acknowledgments The authors thank Dr. M. Asanger for pharmaceutical support and preparation of the capsules, Dr. K. Delport for assistance in preparing the manuscript in English, and Prof. D. Oertli, F.A.C.S., for critical review of the manuscript. The authors declare no financial support.

References

1. Wexner SD, Person B (2006) The management of postoperative ileus. Curr Probl Surg 43:12–65
2. Luckey A, Livingston E, Taché Y (2003) Mechanisms and treatment of postoperative ileus. Arch Surg 138:206–214
3. Miedema BW, Johnson JO (2003) Methods for decreasing postoperative gut dysmotility. Lancet Oncol 4:365–372
4. Kehlet H, Holte K (2001) Review of postoperative ileus. Am J Surg 182:3S–10S
5. Livingston EH, Passaro EP (1990) Postoperative ileus. Dig Dis Sci 35:121–132
6. Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH (2001) 'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic surgery. Br J Surg 88:1533–1538
7. Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbølle P, Hendel HW, Rosenberg J, Kehlet H (2002) Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. Br J Surg 89:446–453
8. Bardram L, Funch-Jensen P, Kehlet H (2000) Rapid rehabilitation in elderly patients after laparoscopic colonic resection. Br J Surg 87:1540–1545
9. Basse L, Madsen JL, Kehlet H (2001) Normal gastrointestinal transit after colonic resection using epidural analgesia, enforced oral nutrition and laxative. Br J Surg 88:1498–1500
10. Wind J, Polle SW, Fung Kon Jin PHP, Dejong CHC, von Meyenfeldt MF, Ubbink DT, Gouma DJ, Bemelman WA (2006) Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg 93:800–809
11. Curry JI, Lander AD, Stringer MD (2004) A multicenter, randomized, double-blind, placebo-controlled trial of the prokinetic agent erythromycin in the postoperative recovery in infants with gastrochisis. J Pediatr Surg 39:565–569
12. Smith AJ, Nissan A, Lanouette NM, Shi W, Guillem JG, Wong DW, Thaler H, Cohen A (2000) Prokinetic effect of erythromycin after colorectal surgery: randomized, placebo-controlled, double-blind study. Dis Colon Rectum 43:333–337
13. Bonacini M, Quiason S, Reynolds M, Gaddis M, Pemberton B, Smith O (1993) Effect of intravenous erythromycin on postoperative ileus. Am J Gastroenterol 88:208–211
14. Kasparek MS, Glatzle J, Mueller MH, Vogt A, Koenigsrainer A, Zittel TT, Kreis ME (2007) Postoperative colonic motility after tropisetron and a standardized meal in patients undergoing conventional colorectal surgery. Int J Colorectal Dis 22:521–529
15. Viscusi ER, Goldstein S, Witkowski T, Andonakakis A, Jan R, Gabriel K, Techner L, Wallin B (2006) Alvimopan, a peripherically acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery. Surg Endosc 20:64–70
16. Wolff BG, Michelassi F, Gerkin TM, Techner L, Gabriel K, Du W, Wallin BA (2004) Alvimopan, a novel, peripherally acting m opioid antagonist. Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. Ann Surg 240:728–735
17. Seta ML, Kale-Pradhan PB (2001) Efficacy of metoclopramide in postoperative ileus after exploratory laparotomy. Pharmacotherapy 21:1181–1186
18. Cheape JD, Wexner SD, James K, Jagelman DG (1991) Does metoclopramide reduce the length of ileus after colorectal surgery? Dis Colon Rectum 34:437–441
19. Jepsen S, Klaerke A, Nielsen PH, Simonsen O (1986) Negative effect of metoclopramide in postoperative adynamic ileus. A prospective, randomized, double blind study. Br J Surg 73:290–291
20. Myrhöj T, Olsen O, Wengel B (1988) Neostigmine in postoperative intestinal paralysis. A double-blind, clinical, controlled trial. Dis Colon Rectum 31:378–379
21. Roberts JP, Benson MJ, Rogers J, Deeks JJ, Wingate DL, Williams NS (1995) Effect of cisapride on distal colonic motility in the early postoperative period following left colonic anastomosis. Dis Colon Rectum 38:139–145
22. Brown TA, McDonald J, Williard W (1999) A prospective, randomized, double-blinded, placebo-controlled trial of cisapride after colorectal surgery. Am J Surg 177:399–401
23. Fanning J, Yu-Brekke S (1999) Prospective trial of aggressive postoperative bowel stimulation following radical hysterectomy. Gynecol Oncol 73:412–414
24. Olsen O, Hakansson T, Forrest JI (1985) Bisacodyl in the treatment of postoperative intestinal atony. Ugeskr Laeger 147:3070–3071
25. Huge A, Kreis ME, Zittel TT, Becker HD, Starlinger MJ, Jehle EC (2000) Postoperative colonic motility and tone in patients after colorectal surgery. Dis Colon Rectum 43:932–939
26. Bodian CA, Freedman G, Hossain S, Eisenkraft JB, Beilin Y (2001) The visual analogue scale for pain: clinical significance in postoperative patients. Anaesthesiology 95:1356–1361
27. Bungard TJ, Kale-Pradhan PB (1999) Prokinetic agents for the treatment of postoperative ileus in adults: a review of the literature. Pharmacotherapy 19:416–423
28. Steadman CJ, Phillips SF, Camilleri M, Talley NJ, Haddad A, Hanson R (1992) Control of muscle tone in the human colon. Gut 33:541–546
29. Beloeil H, Delage N, Negre I, Mazoit JX, Benhamou D (2004) The median effective dose of nefopam and morphine administered intravenously for postoperative pain after minor surgery: a prospective double-blinded isobolographic study of their analgesic action. Anesth Analg 98:395–400
30. Cali RL, Meade PG, Swanson MS, Freeman C (2000) Effect of morphine and incision length on bowel function after colectomy. Dis Colon Rectum 43:163–168
31. Gervaz P, Bucher P, Scheiwiller A, Mugnier-Konrad B, Morel P (2006) The duration of postoperative ileus after elective colectomy is correlated to surgical specialization. Int J Colorectal Dis 21:542–546
32. Graber JN, Schulte WJ, Condon RE, Cowles VE (1982) Relationship of duration of postoperative ileus to extend and site of operative dissection. Surgery 92:87–92
33. Wilson JP (1975) Postoperative motility of the large intestine in man. Gut 16:689–692
34. Bouvet L, Duflo F, Bleyzac N, Mion F, Boselli E, Allaouichiche B, Chassard D (2006) Erythromycin promotes gastric emptying during acute pain in volunteers. Anesth Analg 102:1803–1808
35. Nakabayashi T, Mochiki E, Kamiyama Y, Haga N, Asao T, Kuwano H (2003) Erythromycin induces pyloric relaxation accompanied by a contraction of the gastric body after pylorus-preserving gastrectomy. Surgery 133:647–655
36. Althausen PL, Gupta MC, Benson DR, Jones DA (2001) The use of neostigmine to treat postoperative ileus in orthopedic spinal patients. J Spinal Disord 14:541–545
37. Ferraz AA, Wanderley GJ, Santos MA, Mathias CA, Araújo JG, Ferraz EM (2001) Effects of propranolol on human postoperative ileus. Dig Surg 18:305–310

38. Kalff JC, Schraut WH, Simmons RL, Bauer AJ (1998) Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg 228:652–663
39. Wu FPK, Sietses C, von Blomberg BME, van Leeuwen PAM, Meijer S, Cuesta MA (2003) Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients. Dis Colon Rectum 46:147–155
40. Marret E, Remy C, Bonnet F (2007) Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg 94:665–673
41. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW (2003) Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum 46:851–859
42. Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H (2000) A clinical pathway to accelerate recovery after colonic resection. Ann Surg 232:51–57
43. King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, Kipling RM, Kennedy RH (2006) Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. Br J Surg 93:300–308
44. Hansen CT, Sørensen M, Møller C, Ottensen B, Kehlet H (2007) Effect of laxatives on gastrointestinal functional recovery in fast-track hysterectomy: a double-blind, placebo-controlled randomized study. Am J Obstet Gynecol 196:311.e1–311.e7