Original Article

Randomized Controlled Trial of Bisacodyl Suppository Versus Placebo for Postoperative Ileus After Elective Colectomy for Colon Cancer

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OBJECTIVE: To compare the use of bisacodyl suppository with placebo in resolving postoperative ileus after elective colectomy in a randomized controlled trial.
METHODS: Twenty elective colectomy patients were randomized to receive either bisacodyl or placebo suppository on the third postoperative day. Outcomes included time to first defaecation, length of hospital stay, and postoperative complications. Participants and the primary investigator were unaware of the treatment assignment.
RESULTS: All 10 participants in the bisacodyl group defaecated on the third postoperative day, while participants in the placebo group defaecated on days 3 (2/10), 4 (5/10) and 5 (3/10) ($p < 0.001$). The average lengths of hospital stay for the bisacodyl and placebo groups were 8.5 ± 2.7 days and 10.4 ± 5.3 days, respectively ($p = 0.325$). No significant complications occurred in either group.
CONCLUSION: Bisacodyl suppository seems to be effective and safe in resolving postoperative ileus after elective colectomy in colon cancer patients. [*Asian J Surg* 2007;30(3):167–72]

Key Words: bisacodyl suppository, elective colectomy, postoperative ileus, randomized controlled trial

Introduction

Postoperative ileus is usually defined as a transient impairment of gastrointestinal (GI) motility occurring after surgery and is characterized by abdominal distension, lack of bowel sounds and delayed passage of gas and stool.[1–3] Since postoperative ileus almost always occurs after major abdominal surgery, this condition is sometimes considered a normal response to surgical trauma. Nonetheless, hastening the resolution of ileus might shorten hospital stay and save hospital costs without increasing and perhaps even reducing postoperative morbidity.[1] This may be especially pertinent for patients undergoing colorectal surgery, where the return of colonic function is usually slower than the rest of the GI tract and may be delayed for 3–5 days.[1,4]

Many methods have been used to hasten the resolution of postoperative ileus.[1–3] Few studies have addressed the use of rectal suppository laxatives, however.[1,5] The use of suppository (contact stimulant) laxatives has the advantage of requiring minimal effort on the patient's part, but may adversely affect anastomotic healing due to the vigorous stimulation of bowel movement. A review of 24 patients undergoing elective colectomy at Ramathibodi Hospital in 2003 found that six patients had been treated with bisacodyl suppository. None of these patients had complications attributed to the use of the suppository. One non-randomized study compared the use of bisacolic

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suppository (in addition to oral milk of magnesia) with no laxatives in patients undergoing radical hysterectomy, and found more rapid recovery of bowel function for the former.[5] No complications were observed with the use of bisacolic. However, no randomized controlled studies have been published. The aim of the present study was to compare the use of bisacodyl suppository with placebo in a randomized clinical trial, in terms of time to return of normal bowel function and postoperative complications, in patients with colon cancer undergoing elective colectomy.

Patients and methods

A double-blind, randomized, placebo-controlled clinical trial was performed to assess the efficacy of bisacodyl suppository in hastening the resolution of postoperative ileus following elective colectomy in patients with colon cancer. During the 12-month period between January and December 2005, patients undergoing elective colectomy for colon cancer in the Department of Surgery, Ramathibodi Hospital, were eligible for participation. Inclusion criteria included: age > 18 years; American Society of Anesthesiologist (ASA) classes I to III; failure to defaecate on the third postoperative day. Rectal suppository used to stimulate bowel function was considered on the third day after surgery because most surgeons in our institution felt that it might be unnecessary or unsafe to provide suppositories prior to that time. Exclusion criteria included: evidence of colonic obstruction; carcinomatosis peritonei; refusal to participate.

The primary outcome was the time to defaecation, measured in days, from the day of the primary operation to the first observed passage of stool. Secondary outcomes included the time to audible bowel sounds, defined as the first detection of audible bowel sounds on auscultation, measured from the day of operation; time to flatus, in days, measured similarly but where flatus was defined as passing of bowel gas as reported by the patient; and length of hospital stay, in days. Other outcomes included the number of suppositories provided, time to resumption of oral soft diet, in days, and any observed postoperative complications. These outcomes were recorded and measured by the primary investigator (SW).

Baseline data collected included age, gender, diagnosis, staging of cancer, ASA class and serum potassium level prior to the use of rectal suppository. Treatment-related data included type of operation, operative time, amount of blood loss, types of postoperative analgesics and doses of opioids used.

From a review of a series of 24 elective colectomy patients treated at Ramathibodi Hospital in 2003, the average time to defaecation (for those not treated with bisacodyl suppository) was 5.2 ± 1.3 days. It was hypothesized that bisacodyl suppository given on day 3 after operation would reduce the average time to defaecation by 2 days. To detect this difference with a type I error of 0.05 and a power of 0.9, a sample size of 10 patients per group or 20 patients overall was needed.

Participants were randomized using a computer in blocks of 2 and 4 to one of the two treatment groups. Randomization and allocation sequence were assigned by the statistician (PL) and concealment of allocation was done using sealed opaque envelopes. Research nurses in each ward opened the envelopes on the third postoperative day and assigned participants to their treatment groups, where participants in the treatment group received 10 mg bisacodyl suppository (Dulcolax®; Boehringer Ingelheim GmbH, Ingelheim, Germany) and those in the control group received placebo suppository. The placebo suppository was manufactured at the Faculty of Pharmacy, Mahidol University, to have the consistency and appearance of the bisacodyl suppository. The patient-participants and the primary investigator were unaware of the treatment assignment.

All patients received the same standard preoperative bowel preparation with oral sodium phosphate solution. All patients underwent the same postoperative early ambulation programme. Nasogastric tubes were removed within 24 hours after operation. Patients were usually given morphine sulfate for analgesia. Some also received intravenous parecoxib or pethidine if they could not tolerate the side effects of morphine. No gum chewing was allowed.

If a patient did not spontaneously defaecate on the third day after surgery, s/he was approached by the primary investigator for consent to participate in the research study. If consent was given, a first suppository was applied. If the participant did not defaecate after 12 hours, a second suppository, identical to the first, was applied. After the second suppository, no more were given (Figure). All participants resumed oral intake after defaecation and were followed until hospital discharge.

Note that most surgeons in the study hospital allowed resumption of oral diet according to a fixed protocol, regardless of when defaecation occurred. For this group

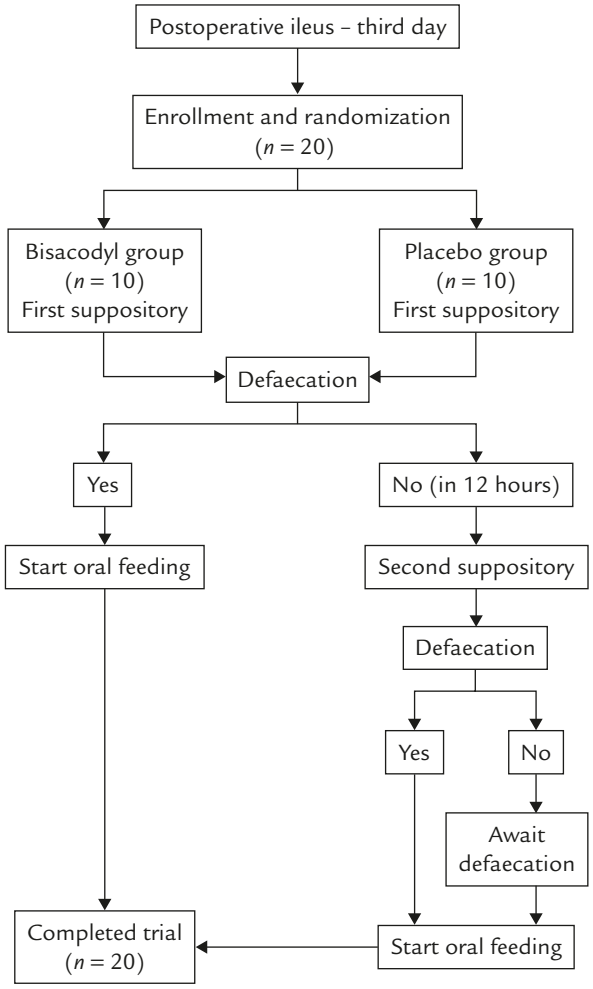

Figure. Trial flow diagram.

of surgeons, all patients were allowed liquid diet on the fifth day after surgery, and soft diet 1 day later, if no complications were suspected by that time. Hence, the time to resumption of oral diet was not a sensitive indicator of the return to normal bowel function in this study.

The study protocol was approved by the hospital's ethics review committee. All participants gave informed consent prior to enrollment into the study.

Continuous data were summarized as mean (standard deviation) or median (range), and categorical and ordinal data were summarized as counts and percentages. Analysis was done according to the intention-to-treat principle. Statistical tests were performed using *t* test or Wilcoxon rank sum test as appropriate for continuous and ordinal variables, and χ^2 or Fisher's exact test as appropriate for categorical variables. Correlation between variables not normally distributed was measured using Spearman's rank correlation. Statistical significance was defined as a *p* value of 0.05 or less. STATA version 7 (Stata Corp., College Station, TX, USA) was used for all statistical analyses.

Results

A total of 20 patients were approached and all consented to participate in the research during the study period. Ten participants received bisacodyl suppository and 10 received the placebo. The flow of patients is illustrated in the Figure. All patients underwent treatment as assigned with no loss to follow-up. Two participants in the control group required a third therapeutic (bisacodyl) suppository on the sixth and eighth postoperative days for abdominal bloating after oral feeding, which occurred after the first defaecation episodes.

Baseline and demographic data are presented in Table 1. These data were comparable between the two treatment groups, with the important exception of the amount of morphine used. A clinically significant larger amount of morphine was used in the control group compared with the suppository group, about twice as much, although this was only marginally statistically significant because of the small sample size (Wilcoxon rank sum test, $p = 0.053$). Although two patients in the suppository group and one in the control group had laparoscopic-assisted colorectal procedures, these patients were part of a "learning curve" experience.

The outcomes of the study are presented and contrasted on an intention-to-treat basis between the two groups in Table 2. The most obvious differences were the timing (day) of defaecation and the number of suppositories used. All participants receiving bisacodyl suppository defaecated on the same day of application, while most patients receiving placebo defaecated 1 or 2 days later. Most participants in the bisacodyl group (90%) received only one suppository. There was no significant difference between the two groups in terms of the time to resumption of oral soft diet.

There was no significant correlation between the amount of morphine used and days to defaecation. The median amounts of morphine used for patients defaecating on days 3, 4 and 5 were 15 mg, 43 mg and 23 mg, respectively. The correlation coefficient for days to defaecation and amount of morphine used was 0.256 ($p = 0.322$). There was only a weak correlation between the amount of morphine used and duration of hospital stay ($r = 0.342$; $p = 0.179$).

Table 1. Baseline and demographic variables in the control ($n = 10$) and treatment ($n = 10$) groups*

Base line variables	Control group	Treatment group
Age (yr)	59.9 ± 12.4	63.8 ± 8.1
Sex (female:male)	4:6 (40:60)	5:5 (50:50)
Location of tumour		
Right side of colon	4 (40)	3 (30)
Left side of colon	1 (10)	1 (10)
Sigmoid colon	5 (50)	6 (60)
Operation		
Right hemicolectomy	4 (40)	3 (30)
Left hemicolectomy	1 (10)	1 (10)
Sigmoidectomy	5 (50)	6 (60)
TNM staging		
Stage I	1 (10)	2 (20)
Stage II	5 (50)	5 (50)
Stage III	4 (40)	3 (30)
ASA class		
ASA II	9 (90)	8 (80)
ASA III	1 (10)	2 (20)
Operation type		
Open	9 (90)	8 (80)
Laparoscopic	1 (10)	2 (20)
Analgesia (intravenous)		
Morphine	8 (80)	7 (70)
Pethidine	0	1 (10)
Morphine + parecoxib	2 (20)	2 (20)
Dose of morphine (mg)	32.0 ± 17.1	16.4 ± 12.7
Median (range)	32 (10–64)	12 (6–44)
Operation time (hr)	3.0 ± 1.1	2.7 ± 1.2
Blood loss (mL), median (range)	200 (100–500)	100 (100–300)
Serum potassium (mmol/L)	3.83 ± 0.31	3.78 ± 0.44

*Data are presented as mean ± standard deviation or *n* (%).

Only two postoperative complications occurred in this study, both in the placebo group. These were all superficial surgical site infections. No anastomotic complications occurred. All participants in the bisacodyl group were able to tolerate oral diet after defaecation. Four participants in the placebo group could not tolerate oral diet after defaecation, and two of these eventually required supplemental bisacodyl suppositories because of persistent abdominal bloating and discomfort.

The average length of hospital stay was 2 days shorter in the bisacodyl group (8.5 *vs.* 10.4 days, a difference of 1.9 days; 95% confidence interval, –2.0 to 5.8 days), but this difference did not reach statistical significance (*t* test, $p = 0.325$).

Discussion

The results of this study showed that defaecation occurred significantly earlier in the group that received bisacodyl suppository, without evident anastomotic complications. Participants in the bisacodyl group were also able to better tolerate oral diet, and were able to leave the hospital 2 days earlier on average, which is a clinically important result. However, the latter difference was not statistically significant.

An unexpected finding was that patients in the control group received twice the amount of morphine as the suppository group. We were unable to find any systematic explanation for this result. Because of the small sample size, this might have been a chance occurrence. Nonetheless, the larger amount of morphine provided to the control group might confound the association between the use of bisacodyl suppository and earlier defaecation. Although this might have been the case, on closer analysis, there was no clear correlation between days to defaecation and amount of morphine used. This lack of correlation implied that the amount of morphine used was unlikely to explain all the association between the use of bisacodyl suppository and earlier defaecation. Similarly, the larger amount of morphine used might have delayed hospital stay, but probably not by much, since this correlation was also weak.

The pathogenesis of postoperative ileus is incompletely understood.[1–3] Neural, hormonal, pharmacological and inflammatory mechanisms, as well as fluid and electrolyte imbalances, all have plausible roles in creating and maintaining the condition.[1–3,6] Postoperative ileus is currently believed to be unnecessary for optimal postoperative recovery, and if prolonged can result in increased complications and costs.[1] Treatment modalities targeted at various potential mechanisms have been met with some success, such as the use of laparoscopic surgery,[7,8] thoracic epidural anaesthesia,[9,10] early feeding (less clear benefit),[11] gum chewing,[4,12,13] the use of certain promotility drugs,[2,14,15] and combinations of the above (multimodality approach).[16,17]

Table 2. Outcome variables in the control ($n = 10$) and treatment ($n = 10$) groups*

Baseline variables	Control group *n* (%)	Treatment group *n* (%)	*p*
Time to audible bowel sounds			0.051†
Day 1	0	2 (20)	
Day 2	8 (80)	8 (80)	
Day 3	2 (20)	0	
Timing of flatus			0.121‡
Day 3 or before	6 (60)	9 (90)	
After Day 3	4 (40)	1 (10)	
Time to defaecation			< 0.001†
Day 3	2 (20)	10 (100)	
Day 4	5 (50)	0	
Day 5	3 (30)	0	
Time to oral intake			0.674†
Day 4	0	3 (30)	
Day 5	3 (30)	0	
Day 6	7 (70)	7 (70)	
Number of suppositories			0.002‡
One tablet	2 (20)	9 (90)	
Two tablets	8 (80)	1 (10)	
Postoperative complications			0.136‡
No	8 (80)	10 (100)	
Yes (surgical site infection)	2 (20)	0	
Length of hospital stay (d)	10.4 ± 5.2	8.5 ± 2.7	0.325§
Median (range)	8 (7–24)	8 (6–15)	0.240†

*Data are presented as *n* (%) or mean ± standard deviation; †Wilcoxon rank sum test; ‡χ^2 test; §*t* test.

Treatments of potential value that can be practically and easily applied for almost all patients include intravenous cisapride, gum chewing and laxatives. Cisapride, a prokinetic drug, administered intravenously to patients undergoing colon surgery has been shown to significantly reduce hospital stay,[2,15] but because of serious adverse cardiovascular effects, it must be used with extreme caution.[18] Gum chewing has been investigated in three randomized controlled trials enrolling patients undergoing colon surgery. Two studies reported no beneficial effects[4,13] while one reported a significant reduction in the length of hospital stay.[12] These results are therefore not conclusive, but gum chewing also requires some effort on the part of the patient. Laxatives have been studied in a non-randomized study in patients undergoing radical hysterectomy.[5] Both orally administered milk of magnesia and bisacolic suppository were used. Significantly earlier return of bowel function and earlier hospital discharge were observed compared with historical controls. To our knowledge, no randomized controlled trials have been conducted to address the benefit of rectally administered laxatives in resolving postoperative ileus.

In theory, the use of suppository laxatives to stimulate bowel activity should be a good method to hasten the resolution of postoperative ileus, especially after colon surgery.[1] The laxative action of rectally administered bisacodyl is almost entirely local, with very little absorption,[19] making this drug quite safe to use in this manner. Using rectal suppositories does not require active participation or effort on the part of the patient, unlike sham feeding methods such as gum chewing. The fear that a vigorous stimulation of the bowel might cause anastomotic dehiscence is probably unfounded as the use of good surgical technique and appropriate suture materials should make the anastomosis resistant to such problems.

The small sample size in this study precluded a more definite statement on whether the use of bisacodyl suppository can reduce hospital stay, and hence hospital costs. Similarly, the absence of any anastomotic complication might also be attributed to the small sample size. The large difference in the amount of opioids used between the two groups in the study is of some concern, but unlikely to explain away all the effects of bisacodyl on the outcomes. The inclusion of laparoscopic-assisted colorectal procedures might have diluted the difference between the two groups, but apparently not enough to affect statistical significance. The selection of colon cancer patients and colonic procedures might not allow generalization to patients operated on for upper gastrointestinal tract diseases. Larger studies are needed to confirm the findings presented in this study, especially the trend in decreasing hospital stay.

In conclusion, bisacodyl suppository seems to be effective in resolving postoperative ileus in colon cancer patients undergoing elective colon resection and may decrease the length of hospital stay without increasing the risk of postoperative complications.

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