Mosapride Reduces Prolonged Postoperative Ileus after Open Colorectal Surgery in the Setting of Enhanced Recovery after Surgery (ERAS): A Matched Case-Control Study

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ABSTRACT

Objective: To evaluate the effects of mosapride, a selective 5-hydroxytryptamine-4 agonist, on gastrointestinal recovery in patients undergoing open colorectal surgery.

Methods: A prospectively collected database of the patients undergoing elective 'open' colorectal resection under enhanced recovery after surgery (ERAS) from May 2013 to April 2017 was reviewed. From April 2016, mosparide was routinely given from postoperative day 1 to discharge date. Eighty-four patients receiving mosapride were matched to 168 control patients (historical comparison with a ratio of 1:2). Surgical outcomes and postoperative gastrointestinal recovery was compared.

Results: The patient characteristics were comparable except more patients in control group had perioperative administration of NSAIDs. The mosapride group had a 1.5% higher compliance rate of ERAS protocol. The control group had higher incidences of prolonged postoperative ileus (17.3% vs 7.1%; p=0.029) and prolonged postoperative ileus requiring nasogastric tube decompression (8.9% vs 3.6%; p=0.19). Overall complication, clinical intestinal transit and length of hospitalization were not significantly different between groups. However, the patients with prolonged postoperative ileus had significantly prolonged hospitalization (p<0.001). Median length of hospital stay was 4 days (IQR 4-5) in those without prolonged ileus (n=217), 5 days (IQR 5-6) in those with prolonged ileus without a need of gastric decompression (n=17) and 10.5 days (IQR 7-14.5) in those with prolonged ileus requiring nasogastric tube decompression (n=18) (p<0.001). A multivariate analysis showed that administration of mosapride was only a protective factor for prolonged postoperative ileus (OR=0.37, 95% CI=0.15-0.93, p=0.029).

Conclusion: Postoperative administration of mosapride reduced the incidence of prolonged postoperative ileus after open colorectal surgery.

Keywords: Mosapride; postoperative ileus; colon; rectum; enhanced recovery after surgery; ERAS; prokinetic drug; prevention (Siriraj Med J 2019;71: 181-188)

INTRODUCTION

Postoperative ileus (POI) is a physiologic hypomotility of the gastrointestinal tract occurring immediately after major abdominal or non-abdominal surgery. The pathophysiology of POI is multifactorial and complex. It is known to be associated with inflammatory, neurological and hormonal responses to surgery.[1] Prolonged POI refers to this gastrointestinal dysfunction continuing

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past the expected timeframe – usually beyond 3 days after laparoscopic abdominal surgery and 5 days after open abdominal surgery.[22] Prolonged POI is one of the most frequent and challenging complications following colorectal surgery especially open procedure[3] because it was associated with increased hospital cost and length of hospital stay.[4] Patients with POI were also more likely to develop other postoperative complications and to be readmitted.[5] The incidences of prolonged POI following colorectal surgery vary widely depending on the definition and cut-off limit.[6] For example, a recent French cohort of colorectal patients undergoing surgery with enhanced recovery after surgery (ERAS) program showed the rate of prolonged POI ranged from 10% for a cut-off of 5 days to 40% for a cut-off of 3 days.[7]

Since treatment options for prolonged POI are limited, several methods of preventing or minimizing POI have been advocated such as laparoscopic surgery[3], epidural analgesia[8], administration of selective cyclooxygenase-2 inhibitors[9], and ERAS pathway.[7] Regarding pharmacological intervention, various prokinetic drugs such as metoclopramide, erythromycin and cisapride have been used to improve postoperative gastrointestinal motility. In a systematic review of the aforementioned agents, only cisapride showed a significant reduction in POI.[10] However, cisapride – a 5-hydroxytryptamine-4 (5-HT4) receptor agonist – was withdrawn from the market worldwide because it caused potentially lethal cardiac arrhythmia via its high affinity blockade of cardiac potassium channel.[11]

Mosapride citrate (mosapride) is another prokinetic drug that selectively activates 5-HT4 receptors on the efferent cholinergic neurons of the gastrointestinal tract, leading to increased acetylcholine release and hence increased bowel contraction – without cardiac side effects.[11] Mosapride has been shown to reduce the duration of POI after hand-assisted laparoscopic colectomy[12] and laparoscopic colectomy.[13] However, its effect on POI after open colorectal surgery has not been assessed especially in the setting of ERAS pathway. The aim of the present study was therefore to evaluate whether mosapride reduced the incidence of prolonged POI and shorten the duration of gastrointestinal recovery after open colectomy and/or proctectomy.

MATERIAS AND METHODS

Patients

This was a review of prospectively collected database of patients undergoing elective 'open' segmental resection (colectomy and/or proctectomy) within an ERAS pathway from May 2013 to April 2017 in the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Patients with clinical peritonitis or acute colonic obstruction were excluded. The study was approved by the institutional ethics committee (Si 014/2013) and written informed consent was obtained from each patient.

ERAS protocol and pharmacologic intervention

All of the studied patients were operated on and treated by a board-certified colorectal surgeon (the author) who has applied an ERAS pathway into colorectal surgery since 2010. ERAS strategies in our institute were adopted from the ERAS society recommendations for perioperative care in elective colorectal surgery.[14,15] Some details of our ERAS program have been described previously.[9,16-18] Briefly, a practice of perioperative pain control with a preferential use of non-opioid analgesia, mechanical bowel preparation for left-sided colon and rectal surgery, prophylactic antibiotic regimen, prophylaxis of postoperative nausea and vomiting, selective use of diverting stoma after colorectal anastomosis, no insertion of nasogastric tube (NGT), early enteral feeding and immediate mobilization was standardized. There was no postoperative administration of laxative and other prokinetic drugs *except* ondansetron and/or metoclopramide for treating postoperative nausea and vomiting. Of note, from 1 April 2016 mosparide (mosapride citrate 15 mg; about 0.75 USD/tablet) was routinely given to every patient three times a day on postoperative day 1 until the patients were discharged. There is no significant change in our ERAS protocol during the study period *except* the routine postoperative administration of mosapride from April 2016.

If patients met the criteria of prolonged POI (defined systematically by the combination of at least two of the following five criteria on or after the fourth operative day: nausea or vomiting, abdominal distension, inability to tolerate oral diet over 24 hours, absence of gas or stool passing over 24 hours, and radiological evidence of ileus)[6], rescue agents such as intravenous metoclopramide and/or suppository bisacodyl would be given for reducing the duration of ileus. For patients with vomiting and distention, the placement of NGT was performed to provide symptomatic relief. The NGT was placed until patients had decreased drainage volume - together with clinical or radiological improvement. Patients would be discharged from the hospital if they had no fever, good appetite, satisfactory gastrointestinal recovery and a good level of ambulation. All of the patients were scheduled for follow-up at 7-10 days and 30 days after an operation.

Data collection

Data including patient characteristics, operative details, and postoperative outcomes were prospectively collected. Patient characteristics included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (CR-POSSUM) score[19], and preoperative nutritional status based on the subjective global assessment (SGA).[20] Operative details included type of operation and operative time. Overall ERAS protocol compliance of each case was determined based on the ERAS society recommendations for perioperative care in elective colorectal surgery.[14,15]

Postoperative outcomes included postoperative complications (graded I-V according to the Clavien-Dindo classification system)[21], time to global resumption of intestinal transit (defined as interval from surgery to the tolerance of solid food intake in association with passage of stool)[22], the incidence of prolonged POI (as aforementioned criteria)[6], the length of postoperative stay, death and readmission within 30 days after the operation. Impact of prolonged POI on postoperative hospitalization was also determined.

Sample size calculation

For 1-to-2 comparison, a minimum sample size of 81 patients in mosapride group and 162 patients in control group was estimated to show a 50% reduction in the incidence of prolonged POI with a power of 90% and a significance level of 0.05.[13] Sample size calculations were based on a recent prospective study in France[22] indicating that 39.6% of patients undergoing colorectal surgery within an ERAS protocol experienced prolonged POI using the clinical definition of prolonged POI purposed by Vather et al.[6] We calculated the sample size based on this French study because a well-established ERAS pathway was fully applied in this French university hospital - like ours. Patients receiving mosapride were matched with historical control patients on potentially confounding factors for prolonged POI such as age, co-morbidity, site of operation (colon vs rectum), stoma formation and extension of surgical treatment.

Statistical analysis

All statistical analyses were performed using the PASW Statistics software (SPSS version 18.0 for Windows, Illinois, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile; IQR), and were compared using the Student t-test or Mann-Whitney U test. Categorical data were expressed as number (percentage) and were compared using the Pearson Chi-square test or Fisher exact probability test. Factors potentially associated with or protective of prolonged POI were analyzed using a univariate analysis. Only significant variables from the univariate analysis were included in a multivariate model of logistic regression (forward stepwise logistic regression analysis), and the odds ratio with 95% confidence intervals (95% CI) for each variable was determined. A p-value of <0.05 was considered statistically significant.

RESULTS

After case-matching from a database of 305 cases, 252 patients were included - 84 in the mosapride group and 168 in the historical control group (Fig 1). Patient characteristics were comparable except more patients in control group had perioperative administration of NSAIDs, and mosapride group had a 1.5% higher compliance rate of ERAS protocol (Table 1). Overall complication, global resumption of intestinal transit and length of hospitalization were not significantly different between the two groups (Table 2). However, the control group had more incidence of prolonged POI and prolonged POI requiring NGT insertion (17.3% vs 7.1%; p=0.029 and 8.9% vs 3.6%; p=0.19), respectively. Clinical factors associated with prolonged POI were shown in Table 3. A multivariate model of logistic regression showed that postoperative administration of mosapride was *only* a protective factor for prolonged POI (OR=0.37, 95% CI=0.15-0.93, p=0.029).

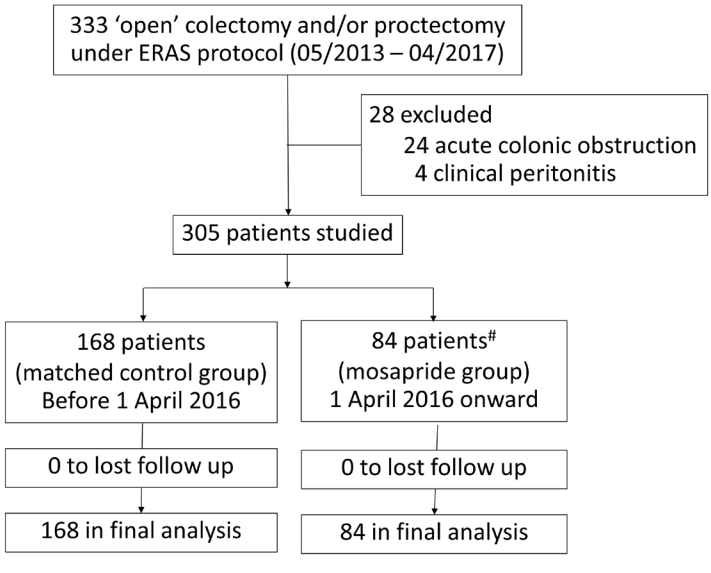

Fig 1. Flow diagram of participant enrollment and analysis.

#There was no patient refusing consent to receive the drug or excluding from analysis

TABLE 1. Patient's characteristics and intraoperative parameters.

	Mosapride (n=84)	Control (n=168)	*P*-value
Age, year	62.4 ± 12.9	64.1 ± 11.8	0.306
Male	44 (52.4)	95 (56.5)	0.531
BMI, kg/m^2	22.6 ± 4.1	22.9 ± 4.1	0.630
ASA class ≥ 3	13 (15.5)	42 (25.0)	0.084
CR-POSSUM predictive mortality, %	1.90 (1.30-2.60)	1.83 (0.98-2.58)	0.426
Hematocrit, %	37.4 ± 5.7	36.8 ± 5.4	0.335
Preoperative malnutrition[#]	16 (19.0)	46 (27.4)	0.148
Previous laparotomy	7 (8.3)	13 (7.7)	0.869
Previous abdominal/pelvic irradiation	6 (7.1)	8 (4.8)	0.437
Cancer surgery	79 (94.0)	152 (90.5)	0.334
Tumor staging ≥ 3	41 (51.9)	89 (57.4)	0.422
Rectal surgery	47 (56.0)	93 (55.4)	0.929
Stoma creation	16 (19.0)	33 (19.6)	0.910
Major multi-organ resection[##]	4 (4.8)	15 (8.9)	0.315
Detailed procedure			0.930
(Extended) right hemicolectomy	13 (15.5)	26 (15.5)	
(Extended) left hemicolectomy	9 (10.7)	8 (4.8)	
Sigmoidectomy	13 (15.5)	36 (21.4)	
Hartmann procedure	7 (8.3)	16 (9.5)	
(Sub) total colectomy	2 (2.4)	6 (3.6)	
(Low) anterior resection	34 (40.5)	65 (38.7)	
Abdominoperineal resection	6 (7.1)	11 (6.5)	
Epidural analgesia	22 (26.2)	41 (24.4)	0.758
Duration of surgery, minute	184 ± 57	189 ± 77	0.577
Blood loss, mL	120 (50-200)	150 (100-250)	0.090
Perioperative administration of NSAIDs	34 (40.5)	91 (54.2)	0.040*
Total IV morphine consumption, mg/kg	0.43 (0-0.71)	0.26 (0.01-0.79)	0.964
Overall ERAS protocol compliance[###], %	83.6 ± 4.4	82.1 ± 4.7	0.010*

*P-value < 0.05

Values are expressed as mean ± standard deviation, median (interquartile range) or number (percentage).

[#]Malnutrition was defined as subjective global assessment (SGA) class B and class C.

[##]Major multi-organ resection excluded the resection of appendix, gallbladder, ovaries and fallopian tubes, small bowel, and part of urinary bladder (partial cystectomy).

[###]Overall compliance of each patient was determined based on the ERAS® society recommendations for perioperative care in elective colorectal surgery.

Abbreviations: ASA = American society of Anesthesiologists, BMI = body mass index, CR-POSSUM = ColoRectal Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, ERAS = enhanced recovery after surgery, NSAIDs = non-steroidal anti-inflammatory drugs

TABLE 2. Postoperative outcomes.

	Mosapride (n=84)	Control (n=168)	*P*-value
Prolonged POI	6 (7.1)	29 (17.3)	0.029*
Prolonged POI requiring NGT insertion	3 (3.6)	15 (8.9)	0.193
Overall complication	12 (14.3)	34 (20.2)	0.249
Serious complication#	4 (4.8)	8 (4.8)	1.000
Time to off intravenous fluid, days	2 (2-3)	2 (2-3)	0.412
Global resumption of intestinal transit, days	3 (2-3.5)	3 (2-4)	0.868
Length of hospitalization, days	4 (4-5)	4 (4-5)	0.474
30-day readmission	1 (1.2)	7 (4.2)	0.275

*P-value < 0.05
Values are expressed as number (percentage) or median (interquartile range).
#Serious complication was defined as the Clavien-Dindo classification of surgical complication grade III-V. Mosapride group had 4 patients with serious complications as following: intraabdominal collection requiring reoperation, adhesive small obstruction requiring relaparotomy, upper gastrointestinal bleeding requiring endoscopic intervention, and distal duodenal obstruction requiring endoscopic management. Control group had 8 patients with serious complications as following: anastomotic leakage (3) requiring reoperation, pelvic collection requiring percutaneous drainage, anastomotic bleeding requiring endoscopic clipping, upper gastrointestinal bleeding requiring endoscopic intervention, and life-threatening congestive heart failure (1) and liver failure (1) requiring intensive care unit management.

Abbreviations: NGT = nasogastric tube, POI = postoperative ileus

TABLE 3. Clinical factors associated with prolonged postoperative ileus (PPOI).

	No PPOI (n=217)	PPOI (n=35)	*P*-value	Odds ratio (95% CI)
Serious complication#	8 (3.7)	4 (11.4)	0.068	3.37 (0.96-11.86)
ASA ≥ 3	44 (20.3)	11 (31.4)	0.138	1.80 (0.82-3.96)
ERAS compliance > 80%	117 (53.9)	15 (42.9)	0.224	0.64 (0.31-1.32)
Administration of NSAIDs	111 (51.2)	14 (40.0)	0.221	0.64 (0.31-1.32)
Administration of mosapride	78 (35.9)	6 (17.1)	0.029*	0.37 (0.15-0.93)

*P-value < 0.05
Values are expressed as number (percentage).
#Serious complication was defined as the Clavien-Dindo classification of surgical complication grade III-V.

Abbreviations: ASA = American society of Anesthesiologists, ERAS = enhanced recovery after surgery, NSAIDs = non-steroidal anti-inflammatory drugs

The length of hospitalization in patients with prolonged POI was significantly longer than those without such a condition (p<0.001). Median length of postoperative stay was 4 days (IQR 4-5) in those without prolonged POI (n=217), 5 days (IQR 5-6) in those with prolonged POI without a requirement of NGT decompression (n=17), and 10.5 days (IQR 7-14.5) in those with prolonged POI requiring NGT decompression (n=18) – which was significantly different between groups (Fig 2).

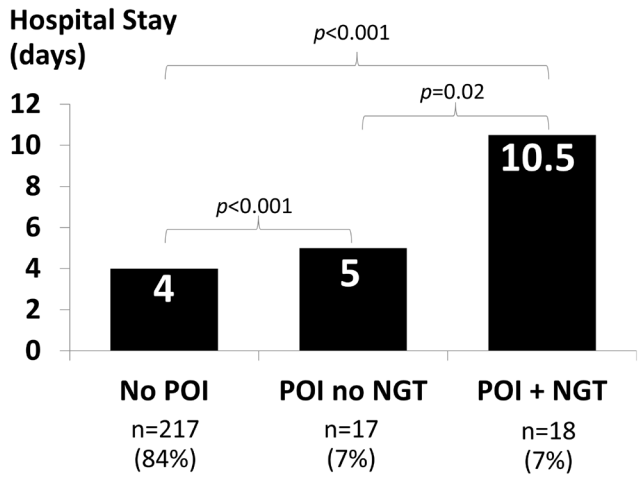

Fig 2. Association between postoperative ileus and length of hospitalization.
Abbreviations: NGT = nasogastric tube, POI = postoperative ileus

DISCUSSION

Prolonged POI is one of the most common problems after intra-abdominal surgery especially open laparotomy. Since treatment options for prolonged POI are limited, preventive measures of POI such as multimodal analgesia[9], application of ERAS pathway[7] and administration of prokinetic drugs are essential.[12,13] This study demonstrated that within an ERAS pathway postoperative administration of mosapride reduced the incidence of prolonged POI after open colorectal surgery. To the best of our knowledge, this is the first clinical study examining the beneficial effects of mosapride on bowel function following open colorectal operation – after its favorable effects on shortening time to gastrointestinal recovery have been shown in hand-assisted laparoscopic colectomy and laparoscopic colectomy for colon cancer.[12,13]

Mosapride is a relatively new prokinetic drug available in Asian countries such as Japan and Thailand. It is a highly selective 5-HT4 receptor agonist facilitating acetylcholine release from the enteric cholinergic neurons within myenteric and submucosal plexus. It has been shown to accelerate gastric emptying rate[12], shorten small bowel transit[23], stimulate colonic motility[24] and augment rectal contraction.[25] Interestingly, in a recent animal study mosapride has been shown to exert anti-inflammatory effects on the muscular wall of gastrointestinal tract after intestinal manipulation and therefore dramatically inhibit POI.[26] Unlike other 5-HT4 receptor agonists such as cisapride and tegaserod, mosparide has no effect on cardiac potassium channels, dopamine receptors or other 5-HT receptors thus resulting in a high profile of safety.[11]

Several prokinetic agents have been used to prevent or reduce POI. Among the most common drugs used are cisapride and metoclopramide. An animal study comparing the prokinetic activities of mosapride with these two drugs showed that all agents promoted gastric emptying but only mosapride enhanced small bowel and large bowel motility in a dose-response relationship.[27] In another animal model, electrointestinography was used to measure intestinal motility after jejunocecostomy. The authors found that bowel motility significantly reduced following surgery. However, in the treated group with mosapride (daily for 5 days after surgery), the contractile amplitude of the small intestine was significantly higher than in the controls indicating that mosapride could overcome the decline of intestinal motility after bowel anastomosis.[28] So far, there have been several animal and human studies supporting the administration of mosapride for facilitating bowel movement or reducing POI after gastrointestinal surgery.[12,13,27,28]

The present study showed that patients receiving mosapride had a lower incidence of prolonged POI and a less requirement of NGT decompression for treating prolonged POI. However, we failed to demonstrate a faster time to global resumption of intestinal transit (time to tolerance of solid food intake *and* passage of stool after an operation) in the mosapride group. The reason for the absence of a significant difference in gastrointestinal recovery between groups could be partly explained by that an ERAS pathway markedly shortens time to postoperative gastrointestinal recovery especially in patients with high compliance[7] – like our patients. Also, the sample size calculation of this study was based on the hypothesis that mosapride could reduce an incidence of prolonged POI by half - not based on time to tolerate solid food or first bowel movement. An ability to tolerate solid food or passing stool may indicate only gastric and rectal emptying and not necessarily the function of the entire gastrointestinal tract. Given the limitations of these individual endpoints, we used a combination of clinical and radiologic grounds for defining prolonged POI as our primary endpoints.[6]

It could be argued that a lower incidence of prolonged POI in mosapride group was associated with a slightly higher compliance of ERAS protocol since ERAS compliance ≥ 85% was shown to be a protective factor for prolonged POI.[7] In our univariate analysis, high ERAS compliance, perioperative use of NSAIDs and administration of mosapride were associated with a lower incidence of prolonged POI. However, in a multivariate analysis the postoperative administration of mosapride was *only* factor associated with a decrease in the incidence of prolonged POI.

The beneficial effects of mosapride on postoperative gastrointestinal recovery in this study (open colorectal

surgery) were in line with the findings of 2 randomized control trials (minimally invasive surgery for colon cancer) by Narita et al[12] and Toyomasu et al.[13] In addition to a decreased incidence of prolonged POI by mosapride in the present study, the two prospective clinical trials revealed that mosapride reduced the duration of POI (i.e. a faster time to first bowel movement). It is worth noting that the present study was conducted within a full ERAS setting whereas the two trials were not - since the scheme of early oral feeding was not applied. Moreover, colorectal operations for malignancy and benign diseases were included in the present study whereas only patients with colon cancer were included in the others. Notably, in all studies mosapride citrate (15 mg tablet three times a day) was given from postoperative day 1 until patients were discharge or a maximum period of 7-10 days.[12,13] It is interesting to determine whether preoperative administration of mosapride will further facilitate postoperative gastrointestinal recovery.

This study revealed that patients experiencing prolonged POI had a significantly longer postoperative stay (e.g. 4 days in no prolonged POI vs 10.5 days in prolonged POI requiring NGT) - which could affect patient's quality of life and increase in-hospital expense.[4] Since the overall incidence of prolonged POI in this study was lower than we expected, the effect of POI on length of hospitalization may be not clearly seen between the study groups. However, prolonged POI remains a challenging clinical reality for achieving early discharge in the ERAS setting. Even in a European university hospital with well-established ERAS protocol, the incidence of prolonged POI requiring NGT decompression was as high as 24.7% and the median length of hospital stay increased from 5 days to 13 days if prolonged POI occurred.[29] We acknowledge that other pharmacological interventions such as perioperative administration of the opioid receptor antagonist alvimopan (12 mg before surgery and 12 mg twice daily until discharge) could reduce POI but this drug is more expensive (63 USD per 12 mg capsule) than mosapride tablet (0.75 USD per tablet).[30] Chewing gum, a cheaper intervention, may be a safe and well tolerated method to reduce POI but the degree of improvement is small and of limited clinical significance.[31]

This study has two major strengths. First, all patients were operated on by single colorectal surgeon under a well-established ERAS program. Moreover, there is no significant change in the ERAS protocol during the study period *except* the routine postoperative administration of mosapride from April 2016. It could suggest that a decreased incidence of prolonged POI in the intervention group is a direct effect of prokinetic drug administration - as shown in our analysis. Second, the criteria for a diagnosis of prolonged POI were defined and sample size was appropriately calculated. A matched case-control analysis was also used in this study.

However, some limitations of this study needed to be addressed. First, it is non-randomized trial which could lead to risk of bias. However, using the validated criteria of prolonged POI and matched case-control analyzing a prospectively collected database with well-established ERAS protocol could in part cover the drawback of non-randomized study and may reflect more realistic estimates of treatment outcomes. We acknowledge that a prospectively randomized controlled trial is a better way to study the effect of this prokinetic drug and the present study could allow for a power analysis to define an appropriately-sized trial in the future. Second, only clinical grounds and radiologic evaluation on or after the fourth operative day were used for diagnosing prolonged POI.[6] Ones could argue that other definitions of prolonged POI and sophisticated methods of assessment e.g. intraluminal pressure and migration of radiopaque markers may be used. Since it is clear that a 'standard' definition and diagnosis of prolonged POI remains elusive[32], we used a widely-accepted and validated clinical definition of prolonged POI based on a recent systematic review and global survey in 2013 due to its simplicity and reproducibility.[6] Third, we recruited only patient undergoing open colorectal surgery. Whether the beneficial effect of mosapride on postoperative gastrointestinal recovery will be evident in other intraabdominal operations needs to be examined. In conclusion, although laparoscopic surgery has become a standard operation for colorectal diseases in many countries, open laparotomy remains a common approach in some regions of the world especially in the developing or underdeveloped areas. Consistent with the findings from laparoscopic colon surgery[12,13], this study demonstrated that postoperative administration of mosapride reduced the incidence of prolonged POI after open colorectal surgery. This prokinetic drug could potentially become a part of ERAS protocol to reduce postoperative ileus.

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Conflict of Interest: The author declares that he has no completing interest.

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