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Continuous administration of ramosetron with patient-controlled analgesia after laparoscopic distal gastrectomy does not delay postoperative bowel function recovery

A prospective, randomized, double-blinded study

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Abstract

Background: Currently, 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists are indicated to slow gastrointestinal motility in the diarrhea-predominant subtype of irritable bowel syndrome. They are commonly used to prevent or treat postoperative nausea and vomiting (PONV) and opioid-induced nausea and vomiting (OINV). We conducted a prospective, randomized, double-blinded study to investigate whether the continuous administration of ramosetron, a selective 5-HT3 receptor antagonist, for preventing PONV and/or OINV after laparoscopic distal gastrectomy (LDG) might influence bowel function recovery.

Methods: Patients scheduled to undergo LDG were randomly assigned to 1 of 3 treatment regimens: no prophylactic ramosetron (Group C); ramosetron 0.6 mg added to 2-day intravenous patient-controlled analgesia (IV-PCA) (Group R0.6); and ramosetron 1.2 mg added to 2-day IV-PCA (Group R1.2). Postoperative recovery profiles of bowel function, incidence of postoperative nausea/vomiting and pain, and perioperative data that affected bowel function recovery were evaluated.

Results: Seventy-three patients completed the study protocol. Parameters associated with postoperative recovery of bowel function, such as time to first flatus, time to first bowel movement, time to first defecation, and time to commencement of soft diet, were not significantly different between the 3 groups. The incidence of nausea 2 to 24 hours after surgery was significantly lower in Group R0.6 (20.0%) and Group R1.2 (12.5%) than in Group C (45.8%) ($P < .022$). The ratio of complete response 2 to 24 hours after surgery was significantly higher in Group R0.6 (80.0%) and Group R1.2 (87.5%) than in Group C (54.2%) ($P < .022$). The incidence of retching 24 to 48 hours after surgery was significantly lower in Group R0.6 (0.0%) and Group R1.2 (4.2%) than in Group C (16.7%) ($P < .043$).

Conclusion: Continuous administration of ramosetron with patient-controlled analgesia to prevent PONV and OINV after LDG did not delay postoperative bowel function recovery.

Abbreviations: 5-HT3 = 5-hydroxytryptamine type 3, IBS-D = diarrhea-predominant subtype of irritable bowel syndrome, LDG = laparoscopic distal gastrectomy, OINV = opioid-induced nausea and vomiting, PONV = postoperative nausea and vomiting.

Keywords: 5-hydroxytryptamine type 3, irritable bowel syndrome, opioid-induced nausea and vomiting, postoperative bowel function recovery, postoperative nausea and vomiting

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1. Introduction

Postoperative nausea and vomiting (PONV) is one of the most common complications related to surgery and anesthesia after laparoscopic surgery. Although PONV is often considered a mild adverse event, in some patients, PONV decreases the quality of postoperative recovery to a great extent. Laparoscopic surgery is a risk factor for PONV in adults.[1] The reported incidence of PONV after laparoscopic surgery varies from 40% to 70% and surpasses the general incidence of PONV (from 20% to 30%) after surgery under general anesthesia.[2–5]

Currently, 5-hydroxytryptamine type 3 (5-HT3) receptor antagonists, such as palonosetron, ramosetron, granisetron, and ondansetron, are commonly used to prevent or treat PONV and opioid-induced nausea and vomiting (OINV). These antagonists block 5-HT3 receptors on the ends of the vagal afferents in the gastrointestinal tract, which send signals directly to the emetic center in the medulla, and they antagonize 5-HT3 receptors on the chemoreceptor trigger zone in the area postrema.[6] On the contrary, 5-hydroxytryptamine (5-HT)

plays an important role in gastrointestinal motility, and plasma 5-HT concentration is abnormally increased in patients with the diarrhea-predominant subtype of c.[7,8] From this perspective, 5-HT$_3$ receptor antagonists have been adopted to mitigate symptoms of diarrhea-predominant subtype of irritable bowel syndrome (IBS-D). Alosetron, the first selective 5-HT$_3$ receptor antagonist that was evaluated for clinical use for IBS-D, has proven more effective than placebo. However, the occurrence of ischemic colitis and severe constipation has limited the widespread use of alosetron.[9] Daily administration of low-dose ramosetron (5 and 10 µg) can relieve IBS symptoms in male and female patients with IBS-D compared with placebo. Although no severe constipation or ischemic colitis has been reported, the occurrence of constipation and hard stool increased in a dose-dependent manner.[10] A recent investigation revealed that ondansetron, a widely used antiemetic with an excellent safety record, significantly improved stool consistency in IBS-D patients compared with placebo.[11]

The use of laparoscopy accelerates the functional recovery after most abdominal surgical procedures.[12] However, laparoscopy is associated with an increased risk of PONV and a frequent use of antiemetics. Although a 5-HT$_3$ receptor antagonist has proven effective in preventing and treating PONV, it has not been elucidated whether the use of a 5-HT$_3$ receptor antagonist as an antiemetic could delay postoperative recovery of bowel function, which is a complication that could offset the advantage of laparoscopic surgery. The fact that certain 5-HT$_3$ receptor antagonists slow gastrointestinal motility in patients with IBS-D increases this possibility. To the best of our knowledge, no reports have evaluated the effects of using a 5-HT$_3$ receptor antagonist as an antiemetic against PONV and/or OINV on bowel function recovery after laparoscopic surgery. Therefore, we conducted a prospective, randomized, double-blinded study to investigate whether continuous administration of ramosetron, a selective 5-HT$_3$ receptor antagonist, to prevent PONV and/or OINV after laparoscopic distal gastrectomy (LDG) might influence bowel function recovery. We also analyzed the perioperative data to determine perioperative factors that affect bowel function recovery in patients with LDG.

2. Patients and methods

This trial was approved by the Institutional Review Board of Seoul St. Mary's Hospital, and the study protocol was registered at a publicly accessible clinical registration site that is acceptable to the International Committee of Medical Journals Editors (http://cris.nih.go.kr, registration number KCT0001324).

2.1. Patients

All consecutive patients undergoing elective LDG between May 2012 and April 2013, aged 18 to 70 years, and in physical status I or II of the American Society of Anesthesiologists (ASA) were eligible for the study. Written informed consent was obtained from all patients before enrollment. Exclusion criteria included functional gastrointestinal disease; medication affecting gastrointestinal motility; administration of antiemetic medication within 24 hours before surgery; addiction to opioids; operations other than gastrectomy or gastrointestinal anastomosis; conversion to open gastrectomy; postoperative leakage at the anastomosis site; duration of operation >5 hours; uncontrolled diabetes mellitus; severe cardiovascular, renal, or hepatic disease; and inability to communicate.

2.2. Surgery

Two experienced surgeons performed LDG with or without minilaparotomy for gastric transection and anastomosis. Either of the following operative techniques was carried out using 5 trocars and carbon dioxide pneumoperitoneum at a pressure of 12 mm Hg.

Laparoscopy-assisted distal gastrectomy (LADG) consisted of laparoscopic and minilaparotomy procedures. To maintain the pneumoperitoneum, the greater and lesser omenta were divided. The D1+α/β or D2 lymph node dissection and truncal vagotomy were performed. After full mobilization of the stomach under laparoscopy, the stomach was removed. The specimens were removed, and either a Billroth I gastroduodenostomy or a Billroth II gastrojejunostomy was performed.[13]

In totally laparoscopic distal gastrectomy (TLDG), the laparoscopic procedure was identical to the procedure mentioned above. After the stomach was fully mobilized and resected, the specimen was placed in a laparoscopic bag and was extracted from the abdominal cavity. Intracorporeal Billroth I, Billroth II, or Roux-en-Y anastomosis was performed for reconstruction.[13]

2.3. Anesthesia

No patient received preanesthetic medication. After anesthetic induction and tracheal intubation, anesthesia was maintained with sevoflurane at 1.5% to 2.5% (inspired concentration), medical air in oxygen (fraction of inspired oxygen=0.5), and intravenous remifentanil at 0.05 to 0.3 µg/kg/min. Neuromuscular blockade was achieved with atracurium infusion at 6 µg/kg/min. Mechanical ventilation was adjusted to maintain an end-tidal concentration of carbon dioxide at 35 to 40 mm Hg. Approximately 6 mL/kg/h Ringer lactate solution was infused during surgery, and 6% hydroxyethyl starch of the same volume as blood loss was infused for intraoperative bleeding. A nasogastric tube was not inserted in any case.

2.4. Group allocation and study protocol

Patients were randomly allocated into the control group (Group C), ramosetron 0.6 mg group (Group R0.6), or ramosetron 1.2 mg group (Group R1.2). A computer-generated random number table with block sizes of 3, 6, 9, and 12 was used for randomization. Preoperative bowel preparation was not performed, and the only overnight fast for the patients was before the operation day.

Every patient received dexamethasone (8 mg) right after tracheal intubation. Approximately 30 minutes before the end of surgery, every patient was administered fentanyl with or without ramosetron through an intravenous patient-controlled analgesia (IV PCA) device. The IV PCA regimen consisted of fentanyl (25 µg/kg) with or without ramosetron (total volume including saline=100 mL), and the device was programmed to deliver 2 mL/h as a basal infusion and 0.5 mL per demand with a 15-minute lockout interval during the first 1 to 2 days after surgery. In patients assigned to Group C, no ramosetron was added to the IV PCA regimen. In patients assigned to Group R0.6 or Group R1.2, 0.6 or 1.2 mg of ramosetron was added to the IV PCA regimen, respectively. An anesthesiologist who was not involved in the anesthetic management of the patient prepared the IV PCA. He received a sealed envelope containing information on the patient group allocation and prepared the IV PCA accordingly. The anesthesiologist who managed the anesthesia for the patient, the operating surgeon, and the

outcome assessor as well as the patient were blinded to the group assignment.

Patients were encouraged to ambulate as soon as possible. Patients began ingesting sips of water on the first postoperative day, continued with clear liquid on the next day and progressed to a soft diet on the third postoperative day. For patients who complained of nausea or vomiting during the postoperative period, metoclopramide (10 mg) was administered as a rescue antiemetic at the discretion of the attending anesthesiologist or the attending physician, both of whom were blinded to the patient group assignment. Fentanyl or meperidine was intravenously injected during the postoperative period if the patient complained of severe pain despite the IV PCA administration or if he or she had persistent pain over a 4 on the visual analogue scale (VAS). Patients were discharged from the hospital when their normal bowel function returned and when they could tolerate the soft diet and abdominal pain for at least 24 hours.

2.5. Outcome measurements

The primary endpoint was the time required for the first passage of flatus after surgery. In addition, the time to first bowel movement, time to first defecation, time to commencement of soft diet, and time to initiation of ambulation after surgery were measured to evaluate postoperative recovery of bowel function. Each patient who participated in the study was asked to fill in the data collection form when he or she returned to the wards. After each patient returned to the wards following anesthetic recovery, the outcome assessor educated each patient on how to fill out the data collection form. The data collection form was collected before patients were discharged from the hospital.

The incidences of nausea and vomiting were assessed by the outcome assessor at the end of each of the 4 assessment periods (0–2, 2–24, 24–48, and 48–72 hours). Nausea was defined as a subjectively unpleasant sensation associated with awareness of the urge to vomit; retching as the labored spasmodic and rhythmic contraction of the respiratory muscles without expulsion of gastric contents; and vomiting as the forceful expulsion of gastric contents from the mouth. A complete response was defined as the absence of nausea, retching, or vomiting. Postoperative pain was also evaluated by the outcome assessor using a VAS ruler (0 = no pain, 10 = the worst imaginable pain) at the end of each of the 4 assessment periods. Fentanyl consumption through PCA, rescue analgesic consumption, and rescue antiemetic consumption were recorded at the end of each assessment period. To calculate the equianalgesic fentanyl dose, 75 mg of meperidine was considered to be 100 μg of fentanyl, without considering cross-tolerance.[14]

2.6. Statistical analysis

The sample size was calculated on the basis of the retrospective data on bowel function recovery after LDG performed in our hospital from 2010 to 2011. The mean time to first passage of flatus after LDG was 2.9 ± 0.7 days. We considered a 20% increase in bowel function recovery by postoperative continuous administration of ramosetron as clinically significant. As 24 patients per group were required (for an alpha value of 0.05 and power of 80%), we decided that a total of 81 patients would be needed to account for a 10% dropout rate.

One-way analysis of variance was used to compare the continuous variables between the 3 groups. Categorical variables were analyzed using the χ^2 test or Fisher exact test. Multiple

linear regression models were used to determine which variables independently predicted time to first flatus. Stepwise selection was conducted on variables found to be significant ($P < .1$) by univariate analysis. Preoperative patient characteristics, intraoperative and postoperative findings associated with surgery and anesthesia, and postoperative PONV data were included in the univariate analysis. A P value of $<.05$ was considered significant. Statistical analysis was performed using SPSS 18.0 for Microsoft Windows (SPSS Inc., Chicago, IL).

3. Results

Among 123 patients eligible for the study, 81 were randomly allocated into 3 groups of 27 patients, and 73 were included in the statistical analysis. Eight patients (3 patients from Group C, 2 patients from Group R0.6, and 3 patients from Group R1.2) withdrew from the study before or during data collection due to the conversion to open surgery or due to a violation of study protocol (Fig. 1). Preoperative patient characteristics and PONV-related history were not different between the 3 groups (Table 1). Intraoperative and postoperative findings associated with surgery and anesthesia showed no difference between the groups (Table 2).

The overall incidence of nausea and vomiting until 72 hours after surgery was 46.6%. Total doses of ramosetron administered during 0 to 24 hours postoperatively were 0.32 ± 0.04 mg in Group R0.6 and 0.61 ± 0.04 mg in Group R1.2. Total doses of ramosetron administered during 0 to 48 hours postoperatively were 0.59 ± 0.01 mg in Group R0.6 and 1.18 ± 0.02 mg in Group R1.2. The incidence of nausea during 2 to 24 hours after surgery was significantly lower in Group R0.6 (20.0%) and Group R1.2 (12.5%) than in Group C (45.8%) ($P < .022$). The ratio of complete response during 2 to 24 hours after surgery was significantly higher in Group R0.6 (80.0%) and Group R1.2 (87.5%) than in C group (54.2%) ($P < .022$). The incidence of retching during 24 to 48 hours after surgery was significantly lower in Group R0.6 (0.0%) and Group R1.2 (4.2%) than in Group C (16.7%) ($P < .043$). The incidence of ramosetron-related adverse events (headache, dizziness) showed no difference between the groups during each assessment period (Table 3).

Parameters associated with postoperative recovery of bowel function, such as time to first flatus, time to first bowel movement, time to first defecation, and time to commencement of soft diet, were not significantly different between the 3 groups. The time to initiation of ambulation after surgery and time of hospital stay showed no difference between the groups (Table 4).

To investigate perioperative factors that affected bowel function recovery in patients with LDG, linear regression analysis was performed. Univariate linear regression with preoperative patient characteristics, intraoperative and postoperative findings, and postoperative PONV data revealed that previous abdominal surgery, LADG versus TLDG, D_2 lymph node dissection, intraoperative amount of crystalloid administration, use of rescue antiemetic during 2 to 24 hours after surgery, and equianalgesic fentanyl dose administered during 0 to 24 hours after surgery were significantly associated with time to first flatus after surgery. Stepwise selection of the variables for multiple regression analysis showed that LADG versus TLDG, intraoperative amount of crystalloid administration, and equianalgesic fentanyl dose administered during 0 to 24 hours after surgery were independently associated with time to first flatus after surgery (R^2, determination coefficient = 0.270) (Table 5). Larger amounts of crystalloid and equianalgesic fentanyl
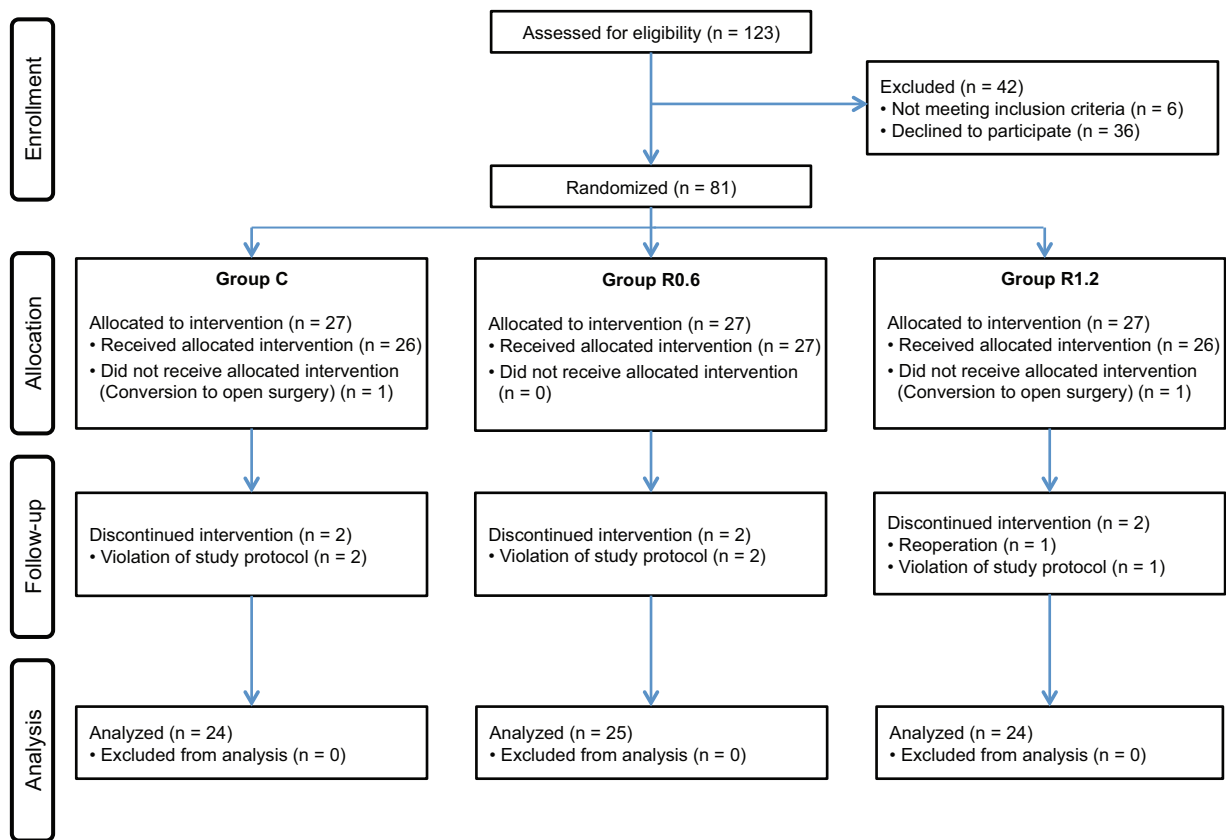
Figure 1. Flow diagram of patient enrollment. Group C, control group; Group R0.6, ramosetron 0.6 mg group; Group R1.2, ramosetron 1.2 mg group.

administration were associated with slower bowel function recovery after surgery. TLDG independently reduced the time to first flatus compared with LADG. However, these 3 factors occupied only 27% of the influence of the time to first flatus after surgery. Two-way interactions between the 3 variables were not significant.

4. Discussion

The results of this randomized trial demonstrate that continuous administration of ramosetron to prevent PONV and OINV after

LDG did not influence the recovery of bowel function. We found that time to bowel function recovery after LDG was independently affected by the dose of postoperative intravenous opioid administration, the amount of intraoperative fluid administration, and whether a LADG or TLDG was performed.

Anesthesia-related substances administered within the perioperative period, including intravenous fluid, opioid analgesics, local anesthetics, β-blockers, acetylcholinesterase inhibitors, vasopressin, magnesium, erythromycin, 5-hydroxytryptamine type 4 receptor agonists, and antiemetics, may significantly impact the postoperative recovery of gastrointestinal motili-

Table 1

Patient characteristics.

	Group C (n=24)	Group R0.6 (n=25)	Group R1.2 (n=24)	P
Age, y	55.0±10.3	54.4±9.1	53.7±9.4	.891
Sex (M/F)	16/8	18/7	16/8	.897
Weight, kg	66.4±11.4	68.2±11.4	63.8±9.8	.370
Height, cm	166.5±7.2	166.5±8.0	165.0±6.9	.727
Body mass index, kg/m^2	23.9±3.0	24.4±2.6	23.3±2.5	.357
ASA physical status (I/II)	9/15	14/11	14/10	.285
Previous abdominal surgery	3	5	3	.774
History of PONV	3	1	0	.213
History of motion sickness	6	3	4	.476
Nonsmoking	19	20	17	.706

Values are expressed as the mean±standard deviation or the number of patients. Group C, control group; Group R0.6, ramosetron 0.6 mg group; Group R1.2, ramosetron 1.2 mg group.
Patient characteristics were not different between the 3 groups.
ASA = American Society of Anesthesiologists, PONV = postoperative nausea/vomiting.

Table 2

Intraoperative and postoperative findings.

	Group C (n=24)	Group R0.6 (n=25)	Group R1.2 (n=24)	P
Type of surgery				.254
LADG	7	13	9	
TLDG	17	12	15	
Type of reconstruction				.417
Billroth I	9	7	7	
Billroth II	10	16	11	
Roux-en-Y	5	2	6	
Lymph node dissection				.368
D1 + α/ β	10	10	14	
D2	14	15	10	
Length of the largest incision, cm	4.23±1.22	4.25±1.36	4.36±0.91	.914
Duration of operation, min	174.5±37.5	183.3±33.8	185.5±44.1	.581
Duration of anesthesia, min	204.7±40.1	215.1±34.8	216.1±45.6	.554
Intraoperative blood loss, mL	90 (50–100)	100 (50–150)	100 (42.5–137.5)	.812
Intraoperative PRC transfusion	0	0	1	.658
Intraoperative amount of fluid administration, mL				
Crystalloid	1175 (1000–1600)	1100 (825–1650)	1175 (925–1600)	.965
Colloid	0 (0–225)	0 (0–0)	0 (0–150)	.390
Intraoperative dose of remifentanil administration, μg	1227±396	1088±467	1042±454	.323
Postoperative				
Early surgical complications[*]				1.000
Anastomotic problem	0	0	0	
Extraluminal bleeding	0	0	0	
Intraabdominal infection	0	0	1	
Wound complication	0	0	1	
Ileus	2	1	1	
Pulmonary problem	1	2	2	
Others[†]	1	1	1	

Values are expressed as the mean ± standard deviation, median (range), or the number of patients. Group C, control group; Group R0.6, ramosetron 0.6 mg group; Group R1.2, ramosetron 1.2 mg group. Intraoperative and postoperative findings were not different between the 3 groups.

LADG = laparoscopy-assisted distal gastrectomy, PRC = packed red cell, TLDG = totally laparoscopic distal gastrectomy.

[*] Complications that occurred within 30 postoperative days.

[†] Others include deep vein thrombosis, spleen infarction, and gout aggravation.

ty.[15,16] Metoclopramide, a traditional and still popularly used antiemetic, has been evaluated for its potential prokinetic influence on gastrointestinal motility by acting as a dopamine antagonist as well as by direct and indirect effects on cholinergic and serotonergic receptors throughout the gastrointestinal tract. Clinical studies have been performed for various types of abdominal surgery; however, none of the studies demonstrated a significant effect of metoclopramide on the postoperative recovery of gastrointestinal motility.[17,18] 5-HT$_3$ receptor antagonists, currently the most popular type of antiemetic, block the 5-HT$_3$ receptors that are widely distributed in both the gastrointestinal tract and the central nervous system. In the intestinal nerves, serotonin acts on the 5-HT$_3$ receptors on the parasympathetic ganglia to cause intestinal smooth muscle contraction and to increase intestinal secretion by stimulating acetylcholine release from nerve terminals.[19] On this basis, a few 5-HT$_3$ receptor antagonists have been adopted as therapeutics for IBS-D to inhibit the acceleration of defecation or diarrhea. However, the effects of 5-HT$_3$ receptor antagonists on the recovery of gastrointestinal motility after abdominal surgery have not been evaluated. In the present study, continuous administration of ramosetron after LDG did not influence the recovery of gastrointestinal motility. Regarding why the use of ramosetron as an antiemetic against PONV and OINV after upper abdominal surgery did not affect postoperative bowel function recovery, the following issues should be considered.

First, inhibitory effects of ramosetron on the gastrointestinal motility could be attributed to the different gastrointestinal pathologies in IBS-D patients. No patient in the present study had functional gastrointestinal disease. The patients underwent gastric resection, gastrointestinal handling, and new gastrointestinal anastomosis, all of which caused temporary postoperative bowel dysfunction. Clinical and animal studies, which support ramosetron as an IBS therapeutic, have been performed in patients with IBS-D symptoms and animals with induced IBS-D symptoms.[10,20,21] Therefore, ramosetron does not seem to further decrease the gastrointestinal motility in patients with temporary bowel dysfunction. A study investigating animals with normal bowel function showed that the administration of ramosetron had no effects on gastrointestinal motility.[21]

Second, the fact that postoperative bowel dysfunction has a multifactorial etiology should be considered. Inflammatory cell activation and autonomic dysfunction caused by surgical resection and manipulation, disruption of intestinal continuity, disturbances of gastrointestinal hormones and neuropeptide, and iatrogenic mechanisms (e.g., opioid analgesia) have been implicated in inducing postoperative bowel dysfunction.[15] Although the degree to which each factor contributes to the induction of postoperative bowel dysfunction has not been scientifically evaluated, the effects of ramosetron on postoperative bowel function could be masked by the above factors.

Table 3

Postoperative nausea/vomiting and pain.

	Group C (n=24)	Group R0.6 (n=25)	Group R1.2 (n=24)	P
Postoperative 0–2 h				
Nausea	8 (33.3%)	10 (40.0%)	7 (30.4%)	.773
Retching	4 (16.7%)	5 (20.0%)	5 (21.7%)	.933
Vomiting	1 (4.2%)	2 (8.0%)	2 (8.7%)	.864
Complete response	16 (66.7%)	15 (60.0%)	16 (69.6%)	.773
Rescue antiemetic	6 (25%)	7 (28.0%)	5 (21.7%)	.882
VAS at rest	3.5±2.1	4.0±2.0	4.4±2.6	.366
VAS at movement	5.6±2.2	6.2±1.9	6.0±2.1	.534
Total equianalgesic fentanyl dose during 0–2 h postop, μg	147±61	148±54	140±77	.888
Headache	3 (12.5%)	2 (8.0%)	4 (17.4%)	.549
Dizziness	2 (8.3%)	2 (8.0%)	3 (13.0%)	.787
Postoperative 2–24 h				
Nausea	11 (45.8%)	5 (20.0%)	3 (12.5%)	.022*
Retching	7 (29.2%)	3 (12.0%)	2 (8.3%)	.178
Vomiting	2 (8.3%)	0 (0.0%)	0 (0.0%)	.210
Complete response	13 (54.2%)	20 (80.0%)	21 (87.5%)	.022*
Total ramosetron dose during 0–24 h postop, mg	0.00±0.00	0.32±0.04	0.61±0.04	<.0001*
Rescue antiemetic	6 (25.0%)	3 (12.0%)	1 (4.2%)	.111
VAS at rest	2.4±1.5	2.8±1.4	2.4±1.7	.483
VAS at movement	4.5±1.6	4.5±1.8	4.5±1.7	.984
Total equianalgesic fentanyl dose during 0–24 h postop, μg	981±278	988±177	959±209	.894
Headache	0 (0.0%)	1 (4.0%)	1 (4.2%)	1.000
Dizziness	4 (16.7%)	5 (20.0%)	4 (16.7%)	1.000
Postoperative 24–48 h				
Nausea	7 (29.2%)	2 (8.0%)	1 (4.2%)	.055
Retching	4 (16.7%)	0 (0.0%)	1 (4.2%)	.043*
Vomiting	3 (13.0%)	1 (4.0%)	1 (4.2%)	.435
Complete response	17 (70.8%)	23 (92.0%)	23 (95.8%)	.055
Total ramosetron dose during 0–48 h postop, mg	0.00±0.00	0.59±0.01	1.18±0.02	<.0001*
Rescue antiemetic	5 (20.8%)	1 (4.0%)	1 (4.3%)	.163
VAS at rest	2.2±4.5	2.5±1.6	1.6±1.3	.124
VAS at movement	4.1±1.9	4.1±2.1	3.9±1.7	.918
Total equianalgesic fentanyl dose during 0–48 h postop, μg	1742±282	1824±298	1733±329	.516
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Dizziness	2 (8.3%)	4 (16.0%)	4 (16.4%)	.757
Postoperative 48–72 h				
Nausea	2 (8.3%)	0 (0.0%)	2 (8.3%)	.385
Retching	2 (8.3%)	0 (0.0%)	2 (8.3%)	.385
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Complete response	22 (91.7%)	25 (100.0%)	22 (91.7%)	.385
Rescue antiemetic	2 (8.3%)	0 (0.0%)	1 (4.2%)	.315
VAS at rest	2.0±1.7	1.8±1.7	1.5±1.1	.527
VAS at movement	3.7±2.1	3.8±2.1	3.4±1.3	.750
Total equianalgesic fentanyl dose during 0–72 h postop, μg	1820±273	1909±323	1831±315	.543
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Dizziness	2 (8.3%)	1 (4.0%)	0 (0.0%)	.537

Values are expressed as the mean±standard deviation or the number of patients (%). Group C, control group; Group R0.6, ramosetron 0.6 mg group; Group R1.2, ramosetron 1.2 mg group.
postop = postoperative; VAS=visual analogue scale.
* P<.05 between the 3 groups.

Third, it could be a matter of dosing. In clinical trials including Asian IBS-D patients, daily oral administration of 5 or 10 μg of ramosetron for 4 to 12 weeks improved diarrhea-dominant IBS symptoms.[10,20] Intravenous administration of 0.3 mg of ramosetron was found to be the most effective dose to prevent and decrease PONV and OINV.[1] In the present study, to be consistent with the maximal dose used in clinical studies, patients in Group R0.6 or Group R1.2 received a continuous infusion of ramosetron at 0.6 or 1.2 mg, respectively, for 1 to 2 days after surgery. We hypothesized that administering a much higher dose of ramosetron to prevent PONV and/or OINV than that used to treat IBS-D symptoms would delay gastrointestinal motility.

However, our study suggests that the effects of ramosetron on gastrointestinal motility seem to be influenced by the period and repetition of administration rather than amount.

In this study, we also investigated perioperative factors that affected bowel function recovery in patients with LDG using multiple regression analysis. We found that LADG versus TLDG, the intraoperative amount of crystalloid administration, and the dose of postoperative intravenous opioid administration were independently associated with the time to first flatus after surgery. These findings are consistent with previous findings on perioperative factors affecting bowel function recovery and the occurrence of postoperative ileus.[22–24] Gao et al[22] reported

Table 4

Postoperative functional recovery.

	Group C (n = 24)	Group R0.6 (n = 25)	Group R1.2 (n = 24)	P
Time to first flatus, d	3.02 ± 0.57	2.86 ± 0.74	2.81 ± 0.96	.608
Time to first bowel movement, d	2.59 ± 0.89	2.52 ± 0.85	2.54 ± 1.17	.966
Time to first defecation, d	3.79 ± 1.16	3.63 ± 1.23	4.17 ± 1.19	.322
Time to commencement of soft diet, d	3.86 ± 0.51	3.99 ± 0.66	4.23 ± 0.84	.182
Time to first ambulation, d	0.92 ± 0.39	0.97 ± 0.54	0.86 ± 0.26	.683
Hospital days, d	7 (7–8.75)	8 (7–9)	7 (8–8.75)	.890

Values are expressed as the mean ± standard deviation or median (range). Group C, control group; Group R0.6, ramosetron 0.6 mg group; Group R1.2, ramosetron 1.2 mg group.

Table 5

Associations of time to first flatus with operative variables through multiple linear regression analysis.

	Univariate regression		Multivariate regression	
	Regression coefficient (SE)	P	Regression coefficient (SE)	P
Previous abdominal surgery	11.427 (5.897)	.057		
Total laparoscopic distal gastrectomy	−8.318 (4.266)	.055	−7.784 (3.816)	.045
D2 lymph node dissection	8.047 (4.2033)	.061		
Intraoperative amount of crystalloid administration, mL	0.013 (0.004)	.001	0.009 (0.004)	.023
Use of rescue antiemetic during 2–24 h postop	0.309 (0.098)	.002		
Equianalgesic fentanyl dose during 0–24 h postop, μg	0.033 (0.0009)	.001	0.027 (0.009)	.003

Postop = postoperative.

that TLDG significantly reduced the time to first flatus compared with LADG. Intraoperative administration of fluid excess also contributes to delayed gastrointestinal motility as a result of the presence of excess fluid in the bowel wall.[23] Perioperative use of opioids is a key contributor to the development of postoperative bowel dysfunction.[24] The gastrointestinal effects of opioids are mediated primarily by the μ receptor, which results in delayed gastrointestinal transit.[25]

Several intraoperative and postoperative factors affect the development of PONV, including surgery itself, the amount of intravenous fluid administration, the use of steroids and opioids, and postoperative pain.[4,26] In the present study, intravenous crystalloid or colloid, remifentanil, and dexamethasone were used for all patients, and the amounts of administration were not different between the 3 groups. Therefore, we assume that they did not influence the incidence of PONV in any particular group.

There are some limitations to our study. First, the time to first flatus after surgery, a primary endpoint in the study, is not an accurate indicator of postoperative bowel function recovery. Measurement of transit time through the small intestine after surgery with a radiopaque marker can be used for accurate assessment of gastrointestinal motility. [27,28] However, time to first flatus is considered an acceptable measurement of gastrointestinal motility in clinical studies in which interventional measurements are rarely allowed. Second, postoperative bowel dysfunction could be much more affected by surgery itself (bowel handling, gastric resection, and anastomosis) than administration of antiemetics. In the present study, 2 experienced surgeons followed a standardized surgical protocol, which we described in the Patients and methods section. Therefore, we assumed identical surgical effects on postoperative bowel function recovery between the 3 groups. Third, the maximal dose of ramosetron used in this study was limited to the maximal acceptable dose, 0.6 mg/day. Administration of

ramosetron at doses of 0.6 mg or more might have yielded different results.

In conclusion, continuous administration of ramosetron with patient-controlled analgesia to prevent PONV and OINV after LDG did not delay postoperative bowel function recovery. It is expected that ramosetron can be used safely after LDG with little concern for postoperative bowel dysfunction. Further studies are necessary to evaluate how the 5-HT3 receptor antagonist administration mode (bolus vs infusion) influences postoperative bowel function recovery.

Author contributions

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