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Effects of prucalopride succinate on postoperative bowel motility and inflammation following minimally invasive gastrectomy

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The enhanced recovery after surgery (ERAS) protocol includes prokinetic agents to reduce postoperative ileus. This double-blind, randomized controlled trial enrolled patients scheduled for minimally invasive gastrectomy for gastric cancer. Patients were randomly assigned to receive either mosapride citrate (control) or prucalopride succinate (experimental) from postoperative days 1 to 4. Bowel motility was assessed by tracking radiopaque marker migration on serial abdominal radiographs, along with first-flatus time, food intake, and inflammatory markers. Baseline characteristics were comparable between groups. The primary endpoint, bowel transit rate on postoperative day 3, showed no significant difference between the control (58.3%) and experimental groups (67.5%, $p = 0.223$). However, on postoperative day 5, the experimental group showed significantly higher colonic transit (96.9% vs. 90.2%, $p = 0.012$) and a greater increase in oral intake over time. The neutrophil-to-lymphocyte ratio (NLR) was significantly lower in the experimental group on POD 3 ($p = 0.035$). Although prucalopride succinate did not accelerate recovery of bowel motility on POD 3, it demonstrated delayed physiological improvement by POD 5 and attenuation of early inflammatory markers, without significant differences in clinical outcomes. Further research is needed to obtain confirmatory evidence before routine incorporation into ERAS protocols.

Enhanced recovery after surgery (ERAS) protocols have been widely adopted in gastrointestinal surgery to promote early recovery, reduce hospital length of stay, and minimize postoperative complications[1–3]. However, postoperative ileus (POI) remains a common problem after major abdominal surgeries such as gastrectomy, often leading to prolonged hospitalization and increased risk of complications such as atelectasis and infection[4].

POI is commonly managed or prevented through the use of prokinetic agents targeting serotonin type 4 (5-HT_4) receptors[5,6]. Nevertheless, recent evidence has demonstrated that mosapride fails to enhance postoperative bowel function after gastrectomy[7]. In contrast to mosapride, prucalopride succinate, a highly selective 5-HT_4 receptor agonist has a primary effect on promoting colonic motility and has been shown to exert anti-inflammatory effects by modulating cholinergic signaling[8,9]. It has demonstrated efficacy in accelerating colonic transit in patients following various gastrointestinal surgeries[10].

These pharmacologic properties make it a suitable agent for addressing POI in the setting of gastric surgery. This randomized controlled trial was conducted to evaluate whether prucalopride improves bowel motility and reduces postoperative inflammation in patients undergoing minimally invasive gastrectomy within an ERAS framework[11,12].

Methods

Study design and ethics

This prospective, double-blind, randomized controlled trial was conducted at Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. The study protocol was approved by the Gangnam Severance Institutional Review Board (IRB No. 2021-0418-006) and complied with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment. The study was registered at ClinicalTrials.gov (NCT05966246) on July 21, 2023. The clinical trial registration was completed post hoc due to an administrative oversight, although all ethical approvals and monitoring were in place.

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Patients

Inclusion criteria included age between 20 and 80 years, histologically confirmed gastric adenocarcinoma prior to surgery, scheduled minimally invasive gastrectomy (laparoscopic or robotic) with curative intent, and American Society of Anesthesiologists (ASA) physical status classification of 3 or lower[13].

Exclusion criteria included distant metastases, evidence of preoperative intestinal obstruction, history of prior chemotherapy, or concurrent malignancy other than gastric cancer. Additional exclusions included history of major abdominal surgery likely to result in extensive adhesions, prior abdominal radiotherapy, hepatic or renal failure due to underlying comorbidities, uncontrolled diabetes mellitus, or known malabsorption syndromes such as inflammatory bowel disease or congenital metabolic disorders[14].

Study withdrawal criteria included requirement for additional bowel resection or extensive adhesiolysis during surgery, conversion to open gastrectomy, inability to resume oral intake postoperatively, or allergic reactions to either prucalopride or mosapride.

Treatment and assessments

Patients were randomly assigned in a 1:1 ratio to receive either prucalopride succinate (experimental group) or mosapride citrate (control group). Mosapride was selected as the control treatment based on findings from a prior randomized study, which showed no significant difference in bowel recovery between mosapride and placebo following minimally invasive gastrectomy[7]. A clinical research coordinator not involved in patient care performed randomization on the day of surgery. Both patients and healthcare providers were blinded to the group allocation.

Control group patients received mosapride citrate (Gasmotin SR®; DaeWoong) 15 mg once daily from postoperative day (POD) 1 to POD 4, while experimental group patients received prucalopride succinate (Resolor®; Janssen Korea) once daily during the same period. Prucalopride dosing was 2 mg for patients under 65 years of age, and 1 mg for those aged 65 or older.

During surgery, a capsule containing 20 radiopaque ring markers (Kolomark™; Intropharm, Korea) was placed at the anastomosis site[15]. Bowel transit time was assessed by counting radiopaque markers visible in the stomach, small intestine, or colon on plain abdominal radiographs obtained on postoperative days 1, 3, and 5 (Fig. 1). Markers passed in stool were considered to have reached the colon.

All patients received perioperative care in accordance with ERAS guidelines, which included standardized anesthetic protocols, goal-directed fluid therapy to maintain near-zero balance, restricted opioid use, avoidance of nasogastric decompression, early initiation of enteral nutrition, and early postoperative mobilization[11]. Epidural anesthesia was not employed.

Patients followed a standardized postoperative dietary protocol consisting of sips of water or carbohydrate fluids on day 1, liquid diet on day 2, and soft diet on day 3, unless limited by patient tolerance.

The primary outcome was bowel transit time, assessed by the percentage of radiopaque markers that had passed into the colon on postoperative day 3.

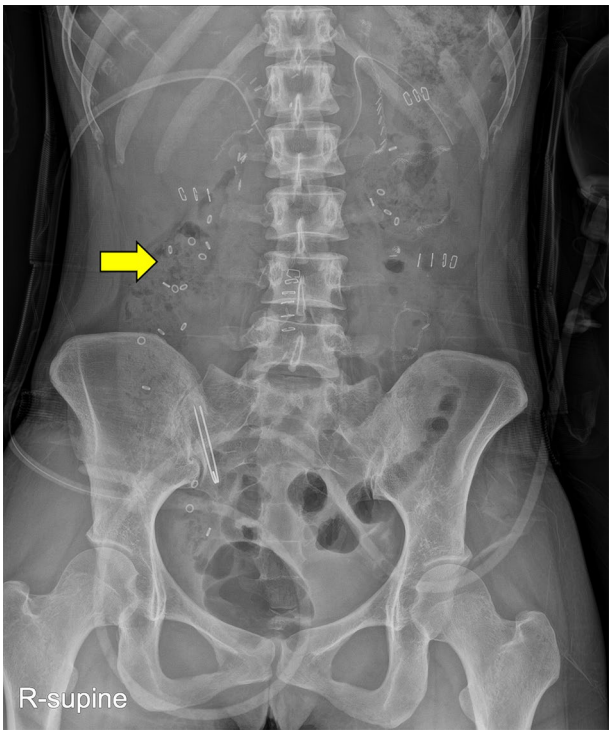


Fig. 1. Radiographic image of radiopaque markers observed in the colon. (Yellow arrow)

Secondary outcomes included time to first flatus, abdominal discomfort assessed using a 5-point numerical scale, proportion of food intake (ratio of food consumed to food provided), and inflammatory markers including C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR)[16,17]. Additionally, postoperative complications were evaluated within 30 days using the Clavien–Dindo classification[18].

To assess potential confounding factors, we compared baseline inflammatory markers (WBC, NLR, CRP), nutritional status (albumin), and pathologic cancer stage between groups according to AJCC 8th edition. Postoperative WBC counts were analyzed as an exploratory inflammatory marker to complement the prespecified NLR analysis.

Statistical analysis

Based on prior data indicating that prucalopride accelerated time to first flatus by approximately 1.37-fold following gastrointestinal surgery[10], we hypothesized a 1.3-fold increase in bowel motility after gastrectomy. To achieve 90% power at a two-sided significance level of 5% while accounting for a 10% dropout rate with 1:1 randomization, a minimum of 53 patients per group was required.

Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean ± standard deviation, and non-normally distributed data as median (interquartile range). Categorical variables are summarized as counts and percentages. Continuous variables were compared using the Student's t-test or Mann-Whitney U test, while categorical variables were analyzed using the chi-square test or Fisher's exact test.

For outcomes measured repeatedly over time, a repeated measures analysis of variance (RM-ANOVA) was employed to evaluate group-by-time interactions. The sphericity assumption was assessed; when violated, Greenhouse–Geisser correction was applied. RM-ANOVA was used to assess the overall difference across time points (between-group effect) and whether temporal patterns of change differed between groups (group-by-time interaction effect).

A p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

In total, the planned 106 patients were enrolled between January 2022 and June 2023. Patients were randomly assigned, with 53 patients allocated to each group. There were no dropouts from the control group, while two patients dropped out of the prucalopride group. One patient withdrew consent, and another was excluded following reoperation (Fig. 2).

A total of 104 patients were included in the statistical analysis. Baseline characteristics, including age, sex, medical history, type of operation, and estimated blood loss, were comparable between the two groups. Baseline laboratory values, including white blood cell count, neutrophil-to-lymphocyte ratio, C-reactive protein, and albumin level, were also similar between groups, indicating balanced inflammatory and nutritional status at baseline. Pathologic TNM staging was also analyzed and was similarly distributed between groups ($p = 1.000$) (Table 1).

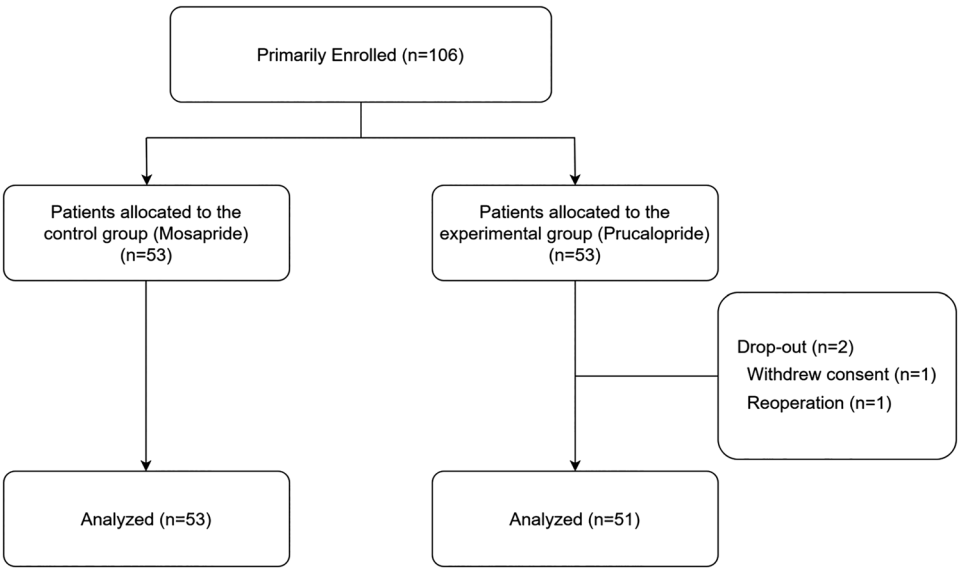


Fig. 2. CONSORT flow diagram of patient enrollment, randomization, analysis.

Characteristics	Control ($n=53$)	Experimental ($n=51$)	p-value
Age (years)*	61.0 (53.0–69.5)	58.0 (46.0–69.0)	0.539
Sex			> 0.999
Male	28 (52.8%)	27 (52.9%)	
Female	25 (47.2%)	24 (47.1%)	
ASA score			0.615
I	3 (5.75)	2 (3.9%)	
II	35 (66.0%)	38 (74.5%)	
III	15 (28.3%)	11 (21.6%)	
BMI (kg/m2)	23.46 ± 3.47	23.95 ± 3.39	0.464
Preoperative laboratory values			
Total White blood cell ($\times 10^2/\mu L$)	6.20 ± 1.47	6.19 ± 1.76	0.995
Neutrophil ($\times 10^2/\mu L$)	5.54 ± 3.14	5.12 ± 3.61	0.536
Lymphocyte ($\times 10^2/\mu L$)	1.70 ± 0.73	1.87 ± 0.93	0.286
NLR	3.99 ± 3.11	3.84 ± 3.92	0.839
C-reactive protein (mg/L)	1.39 ± 2.30	1.92 ± 6.85	0.597
Albumin (g/dL)	3.86 ± 0.50	3.89 ± 0.51	0.795
Prior abdominal surgery (%)	13 (24.5%)	11 (21.6%)	0.817
Estimated blood loss (cc)	55.64 ± 48.62	43.69 ± 43.91	0.192
Operation time (min)	178.30 ± 35.67	173.37 ± 31.18	0.663
Operation method			> 0.999
Laparoscopic	44 (83.0%)	42 (82.4%)	
Robotic	9 (17.0%)	9 (17.6%)	
Type of resection			0.787
Subtotal gastrectomy	44 (83.0%)	44 (86.3%)	
Total gastrectomy	9 (17.0%)	7 (13.7%)	
Anastomosis type			0.874
B-I	18 (34.0%)	19 (37.3%)	
B-II	16 (30.2%)	13 (25.5%)	
STG R-Y	10 (18.9%)	12 (23.5%)	
TG R-Y	9 (17.0%)	7 (13.7%)	
TNM Cancer Staging			1
I	43 (81.1%)	42 (82.4%)	
II	5 (9.4%)	5 (9.8%)	
III	5 (9.4%)	4 (7.8%)	

Table 1. Patient characteristics. *Age is presented as median (interquartile range) because the distribution was non-normal; p-value was calculated with the Mann-Whitney U test. *ASA* American Society of Anesthesiologists physical status score; *BMI* Body mass index; *B-I* Billroth I; *B-II* Billroth II; *STG R-Y* Subtotal gastrectomy Roux-en Y; *TG R-Y* Total gastrectomy Roux-en Y.

Motility evaluation

Bowel motility was assessed in 100 patients (50 control, 50 experimental) after excluding four patients with missed radiopaque marker insertion during surgery. In cases where five or more of the 20 radiopaque marker rings remained impacted at the stomach or anastomosis site, those rings were excluded from the denominator. Significant differences in bowel motility between the two groups were observed on postoperative day 5. On POD 3, the mean percentage of markers that migrated to the colon was 58.25 ± 38.25% in the control group and 67.53 ± 37.47% in the experimental group ($p=0.223$). On POD 5, the corresponding values were 90.20 ± 15.29% and 96.90 ± 10.15%, respectively ($p=0.012$) (Table 2; Fig. 3).

Food intake proportions showed no significant differences between the two groups on POD 3 and POD 5. On POD 3, the control group consumed 61.89 ± 16.30% of provided food, while the experimental group consumed 62.25 ± 21.01% ($p=0.921$). On POD 5, food intake was 61.42 ± 19.30% in the control group and 67.94 ± 20.79% in the experimental group ($p=0.100$).

The abdominal discomfort scores (NRS 1–5) showed no significant differences between the groups throughout the postoperative period. On POD 3, the abdominal discomfort score was 3.53 ± 1.15 in the control group and 3.52 ± 1.29 in the experimental group ($p=0.996$).

Time to first flatus was slightly shorter in the experimental group (68.30 ± 13.46 h) compared with the control group (74.97 ± 20.58 h), with borderline statistical significance ($p=0.053$).

For time-course analyses, RM-ANOVA evaluated both between-group differences and group-by-time interactions. For the primary endpoint (marker transit to colon), a trend toward between-group difference was

	Control group ($n=53$)	Experimental group ($n=51$)	p-value
Percentage of markers in colon (%)			
POD1	0.10 ± 0.71	1.20 ± 8.49	0.363
POD3	58.25 ± 38.25	67.53 ± 37.47	0.223
POD5	90.20 ± 15.29	96.90 ± 10.15	0.012
Proportion of food intake (%)			
POD2	62.45 ± 24.25	56.67 ± 23.47	0.219
POD3	61.89 ± 16.30	62.25 ± 21.01	0.921
POD4	62.74 ± 18.41	66.47 ± 17.42	0.291
POD5	61.42 ± 19.30	67.94 ± 20.79	0.1
Abdominal discomfort scale (NRS 1–5)			
POD1	2.94 ± 1.31	2.76 ± 1.19	0.469
POD2	3.55 ± 1.37	3.41 ± 1.47	0.628
POD3	3.53 ± 1.15	3.52 ± 1.29	0.996
POD4	3.26 ± 1.09	3.14 ± 1.02	0.543
POD5	2.79 ± 1.04	2.69 ± 0.84	0.569
First flatus time (hour)	74.97 ± 20.58	68.30 ± 13.46	0.053

Table 2. Clinical outcome associated with the gastrointestinal motility. *POD* postoperative day.

observed ($p=0.072$) without significant interaction ($p=0.343$), suggesting that the experimental group may have had consistently higher transit with similar rates of change over time. Food intake showed significant group-by-time interaction ($p=0.049$) with progressive increases in the experimental group (Fig. 3).

Postoperative outcomes

We observed no significant differences in the incidence or severity of postoperative complications between the two groups (Table 3). Among the 104 patients, 24 (23.1%) experienced Clavien-Dindo grade I complications, and 49 (47.1%) experienced grade II complications, with similar distributions across groups. Infective complications requiring antibiotic treatment occurred in 4 patients (3.8%), with no significant difference between groups (1 patient [2.0%] in the experimental group vs. 3 patients [5.7%] in the control group, $p=0.618$). No adverse events related to prucalopride administration, including headache, allergic reactions, or hepatic dysfunction, were observed[19]. No major complications such as anastomotic leakage, intra-abdominal abscess, or sepsis occurred in any patient.

CRP levels showed a similar trend with no significant differences on POD 1, 3 and 5. In contrast, the neutrophil-to-lymphocyte ratio (NLR) demonstrated a greater postoperative decrease in the experimental group. Although NLR values on POD 1 were comparable between groups (6.93 ± 2.77 vs. 6.34 ± 3.28, $p=0.330$), the experimental group showed significantly lower NLR on POD 3 (4.85 ± 2.49 vs. 6.02 ± 3.06, $p=0.035$), with a marginal difference remaining on POD 5 (3.33 ± 1.47 vs. 3.91 ± 1.62, $p=0.059$) (Table 3). RM-ANOVA on NLR revealed a significant between-group difference ($p=0.049$), though the group-by-time interaction was not significant ($p=0.420$) (Fig. 3).

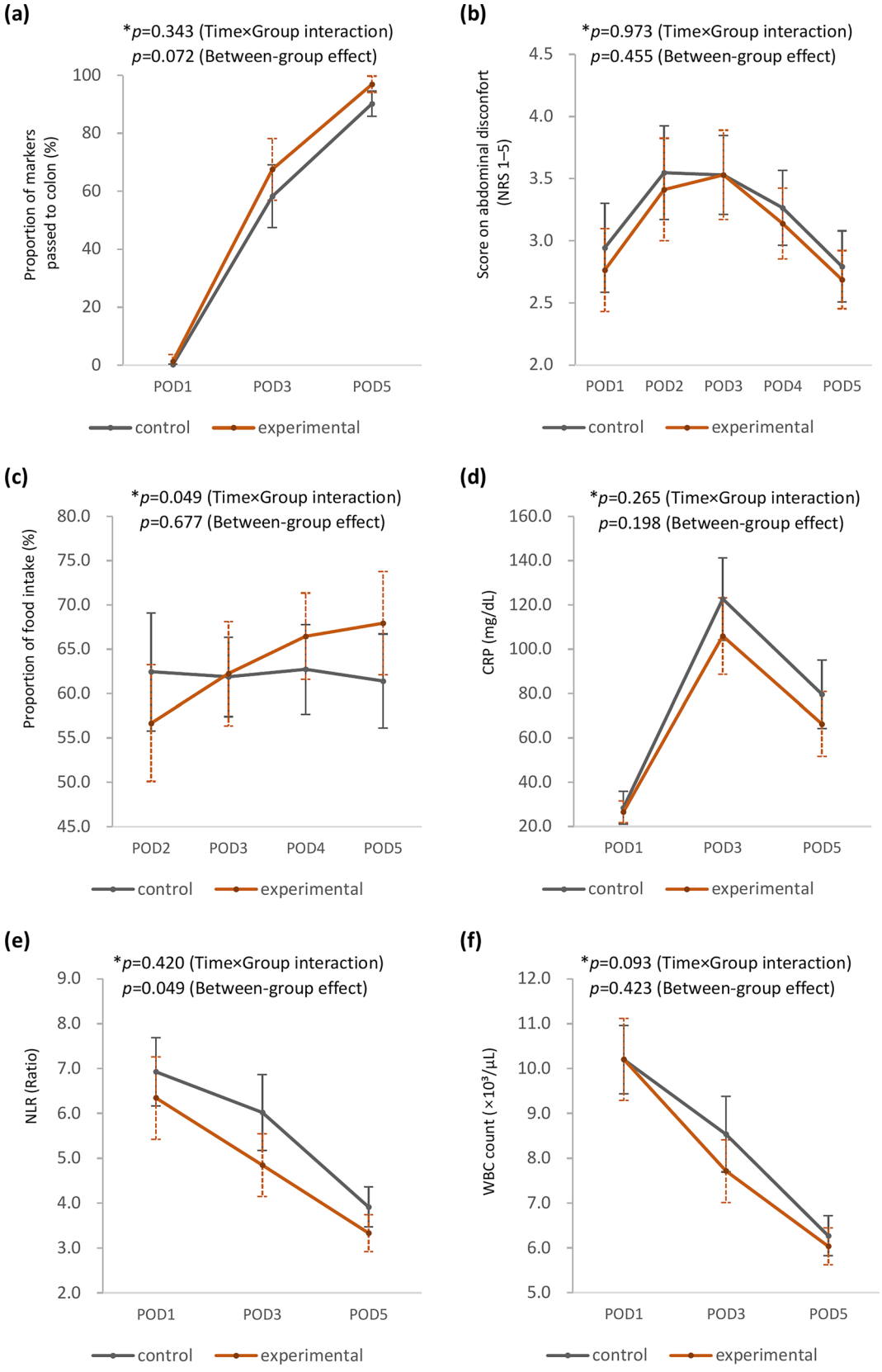
The number of opioid injections and the length of postoperative hospital stay were similar between the two groups (3.25 ± 2.93 vs. 2.51 ± 2.27, $p=0.156$; 5.45 ± 1.10 vs. 5.33 ± 0.59 days, $p=0.494$).

Discussion

In this randomized clinical trial within an ERAS framework, prucalopride was associated with faster recovery of bowel motility and a greater reduction in systemic inflammation compared with mosapride. Although the predefined primary endpoint on POD 3 was not met, prucalopride led to a significant improvement in colonic transit by POD 5 and was accompanied by a progressive increase in oral intake over time, which is a key component of functional recovery after gastric surgery. Although ERAS protocols recommend the use of prokinetic agents, the strength of recommendation has been weak due to limited evidence from randomized trials. Our findings may add to the clinical evidence suggesting that prucalopride could serve as a physiological adjunct within ERAS-based postoperative care after minimally invasive gastrectomy.

The improvement of bowel transit observed with prucalopride may be attributed to its distinct pharmacological profile. Unlike mosapride, which enhances gastrointestinal motility mainly through vagal stimulation of the pylorus, which is resected during gastrectomy, prucalopride exhibits high selectivity for 5-HT_4 receptors and enhances colonic motility, which is particularly relevant in the setting of gastrectomy[20–24].

5-HT_4 receptor activation by prucalopride can stimulate cholinergic anti-inflammatory pathways through α7 nicotinic acetylcholine receptors on muscularis macrophages, potentially reducing early inflammatory responses[25,26]. This mechanism may explain the significantly lower NLR observed in the prucalopride group on POD 3, as NLR reflects early neutrophilic inflammation, while CRP levels—which peak later in the inflammatory cascade—showed no significant differences between groups[27]. The anti-inflammatory effect was further supported by repeated-measures analysis, which demonstrated a significant overall between-group difference in NLR ($p = 0.049$) throughout the postoperative period.



A previous randomized controlled trial also investigated the effects of prucalopride on postoperative gastrointestinal recovery in patients undergoing various types of gastrointestinal surgery, including ileocecal resection, colectomy, and gastroduodenal surgeries[11]. In the prior study, the experimental group receiving prucalopride showed significantly faster recovery of bowel motility, compared to the placebo group, which is consistent with the results of our study. However, the majority of patients (79 out of 110, 71.8%) underwent surgery via laparotomy rather than a minimally invasive approach. Therefore, while the findings support the

◀**Fig. 3**. Postoperative clinical outcomes in the control and experimental groups. **a** Proportion of radiopaque markers that had reached the colon. **b** Abdominal discomfort on a 5-point numerical rating scale (1 = no discomfort, 5 = worst possible discomfort). **c** Oral food intake, expressed as the percentage of the food provided. **d** Serum C-reactive protein (CRP, mg/L). **e** Neutrophil–to-lymphocyte ratio (NLR). **f** White blood cell count ($\times 10^2/\mu L$). Data are presented as mean ± 2 × standard error of the mean (SEM), which approximates the 95% confidence interval for each time-point. **p*-values reflect between-group and group-by-time interaction effects determined by repeated-measures ANOVA. *CRP*, C-reactive Protein; *NLR*, Neutrophil-to-lymphocyte ratio; *NRS*, numerical rating scale; *POD*, postoperative day

Postoperative complication (*n*)	Control group (*n* = 53)	Experimental group (*n* = 51)	*p*-value
Grade I	10 (18.9%)	14 (27.5%)	0.143
Grade II	22 (41.5%)	27 (52.9%)	
Grade IIIa	1 (1.9%)	1 (2.0%)	
CRP level (mg/dL)			
POD1	28.49 ± 27.10	26.57 ± 17.68	0.671
POD3	122.73 ± 67.71	105.97 ± 61.70	0.191
POD5	79.60 ± 56.22	66.28 ± 52.03	0.213
Neutrophil-to-lymphocyte ratio			
POD1	6.93 ± 2.77	6.34 ± 3.28	0.33
POD3	6.02 ± 3.06	4.85 ± 2.49	0.035
POD5	3.91 ± 1.62	3.33 ± 1.47	0.059
White blood cell count ($\times 10^2/\mu L$)			
POD1	10.20 ± 2.61	10.20 ± 2.75	0.995
POD3	8.53 ± 3.17	7.71 ± 2.65	0.155
POD5	6.27 ± 1.77	6.03 ± 1.66	0.489
Albumin level (g/dL)			
POD5	3.38 ± 0.25	3.37 ± 0.27	0.924
Postoperative opioid injection (n)	3.25 ± 2.93	2.51 ± 2.27	0.156
Postoperative hospital stays (day)	5.45 ± 1.10	5.33 ± 0.59	0.494

Table 3. Laboratory Findings and Postoperative Course. *POD* postoperative day, *CRP* C-reactive Protein.

efficacy of prucalopride, the clinical setting differed from our study, which was conducted entirely within the framework of an ERAS protocol incorporating minimally invasive gastrectomy.

Our findings suggest that prokinetic agents may be more effective when targeting gastrointestinal segments that remain intact after surgery. For instance, mosapride, which enhances gastric and duodenal motility, has shown efficacy in patients undergoing colectomy, where the upper gastrointestinal tract remains intact[28]. Conversely, in this study with gastrectomy patients where the pylorus and gastric antrum are removed, prucalopride—a colonic prokinetic—demonstrated superior outcomes. This highlights the importance of comprehensive motility recovery, not only small bowel function, in the management of postoperative ileus.

Several limitations warrant mention. First, this single-center study was conducted in an ethnically homogeneous population, limiting generalizability to other institutions or diverse populations. Second, although improvements were observed in objective markers such as time to first flatus, radiopaque marker transit, and neutrophil-to-lymphocyte ratio, no significant differences were found in hospital length of stay or complication rates between groups. Notably, however, the experimental group demonstrated progressive increases in food intake over time ($p = 0.049$), suggesting potential practical benefits in functional recovery. Third, perfect blinding was challenging due to differences in pill appearance, although both drugs were similarly sized pink tablets dispensed immediately by independent nurses. Blinding effectiveness was not formally assessed through post-study questionnaires. This may have affected subjective outcomes but is unlikely to have influenced objective endpoints such as radiographic marker counts or NLR values. Lastly, trial registration at ClinicalTrials.gov was completed after enrollment began due to an administrative oversight. However, the study protocol, primary endpoint, and statistical analysis plan were fully prespecified and IRB-approved before enrollment began, ensuring that study design and analytical approaches were not influenced by observed outcomes.

Despite these limitations, this prospective, randomized controlled trial provides exploratory evidence on the potential role of prucalopride in postoperative recovery after minimally invasive gastrectomy.

In conclusion, prucalopride demonstrated delayed improvement in intestinal motility, a progressive increase in oral intake, and attenuation of early inflammatory markers following minimally invasive gastrectomy, without significant differences in clinical outcomes. Further research is needed to obtain confirmatory evidence before routine incorporation into ERAS protocols.

Data availability

Datasets used and/or analyzed are available from the corresponding author on reasonable request.

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Author contributions

Shiyeol Jun: Data collection, statistical analysis, writing—edited manuscript, submission; Seyeol Oh: Conceptualization, methodology, investigation, data collection, writing—original draft; Ji Eun Jung: Data collection, statistical analysis; Sung Hoon Noh: Supervision, project administration; In Gyu Kwon: Conceptualization, supervision, funding acquisition, project administration, writing—review and editing, surgical procedures for enrolled patients, corresponding author.Shiyeol Jun and Seyeol Oh contributed equally to this work as co-first authors.

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Declarations

Competing interests
The authors declare no competing interests.

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