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Original Article

ORIGINAL ARTICLE

# Effect of Wuda granule on gastrointestinal function recovery after laparoscopic intestinal resection: a randomized–controlled trial

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## Abstract

**Background** Previous studies have suggested that the Wuda granule (WDG) could promote the recovery of gastrointestinal (GI) function after gynecologic abdominal surgery. This trial aimed to investigate the efficacy and safety of WDG in the rapid recovery of GI function in patients after laparoscopic intestinal resection in the setting of enhanced recovery after surgery (ERAS)-based perioperative care.

**Methods** We performed a randomized, double-blind, placebo-controlled pilot trial. Thirty patients who met the inclusion criteria were randomly assigned to either the WDG group or the placebo group in a 1:1 ratio. The patients received WDG or placebo twice a day in addition to ERAS-based perioperative care, starting on post-operative Day 1 until Day 3. The primary outcomes were time to first bowel movement and time to first tolerance of solid food. The secondary outcomes were time to first flatus, length of hospital stay (LOS), and post-operative ileus-related morbidity. Adverse events were also recorded.

**Results** There were no statistically significant differences in baseline characteristics between the two groups. The median time to first bowel movement was significantly decreased in the WDG group compared with the control group (27.6 vs 50.1 h; $P < 0.001$), but the median times to first flatus (22.9 vs 25.1 h; $P > 0.05$) and LOS (5.0 vs 5.0 days; $P > 0.05$) were not statistically different. The occurrence rates of post-operative nausea, vomiting, abdominal distension, and abdominal pain were similar in the two groups. No adverse events occurred in any patients.

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**Conclusions** The addition of WDG to ERAS post-operative care after laparoscopic intestinal resection can safely promote the rapid recovery of GI function.

**Key words:** Wuda granule; laparoscopic intestinal resection; post-operative gastrointestinal function; ERAS

## Introduction

Gastrointestinal (GI) dysfunction, mainly intestinal paralysis, often occurs after abdominal surgery [1]. Delayed post-operative recovery of GI function after surgery may induce related complications, such as nausea, vomiting, or paroxysmal abdominal pain and progressive abdominal distension [2]. Post-operative ileus (POI) is a transient cessation of coordinated bowel motility that occurs universally after intestinal resection. POI prevents effective transit of intestinal contents and tolerance of dietary intake, which may lead to patient discomfort, morbidity, and prolonged post-operative length of stay (LOS) [3]. Rapid recovery of GI function after surgery is important [4] but effective intervention measures are lacking.

Sham feeding can stimulate bowel motility and chewing gum may elicit the same response as sham feeding by mimicking food intake. Previous studies have shown that chewing gum can reduce the time to first flatus and the time to first bowel movement; however, these studies did not include enhanced recovery after surgery (ERAS)-based perioperative care [5]. The ERAS Society designed a multimodal perioperative care pathway to enhance recovery after abdominal surgery [6–9]. However, one study conducted in the setting of ERAS-based perioperative care suggests that the addition of chewing gum to an ERAS-based post-operative care pathway after elective abdominal surgery does not reduce the LOS or time to bowel recovery [10]. Ho *et al.* [11] also found that chewing gum conferred no advantage if patients were placed on a rapid post-operative feeding regimen, which is an important part of the ERAS protocol. Studies have also shown that alvimopan (a peripherally acting mu-opioid receptor antagonist) has potential benefits for the recovery of GI function after intestinal resection in patients who receive patient-controlled analgesia [12]. However, the guidelines recommended alvimopan to promote post-operative recovery after open colorectal surgery; the effect of alvimopan in minimally invasive surgery remains less clear [13].

Our research team has conducted a series of studies on post-operative GI motility disorder, which is believed to be due mainly to Qi deficiency and Qi stagnation (their clinical manifestations are mainly spiritlessness, fatigue, no bowel movement after surgery, pale tongue, and weak pulse) from the perspective of traditional Chinese medicine [14]. Our team has developed a Wuda granule (WDG), a traditional Chinese herbal medicine, which may promote post-operative recovery of GI function and has obtained a patent granted by the State Intellectual Property Office of People's Republic of China (ZL201410778958). WDG was previously known as Xiangbin prescription, but it was renamed WDG when it became our in-hospital preparation of our hospital in 2018. WDG is composed of Panax Ginseng (Renshen), Arecae Semen (Binlang), Persicae Semen (Taoren), Linderae Radix (Wuyao), and Fructus Amomi (Sharen). Previous studies have shown that WDG can significantly improve weakened gastrointestinal motility after abdominal surgery in dogs [15] and enhance gastric antrum motility via the intramuscular interstitial cells of Cajal in mice [16]. Moreover, WDG can promote duodenal and jejunal movement, and increase plasma concentrations of motilin and ghrelin in healthy volunteers [17], and it has also been shown to promote recovery of GI function after gynecologic abdominal surgery [18].

We hypothesized that WDG would accelerate the rapid recovery of GI function after laparoscopic intestinal resection in the setting of ERAS-based perioperative care. Therefore, we performed a randomized, double-blind, placebo-controlled pilot trial to investigate the efficacy and safety of WDG in the rapid recovery of GI function in patients after laparoscopic intestinal resection in the setting of ERAS-based perioperative care.

## Patients and methods

### Design

This randomized, double-blind, placebo-controlled, parallel-group pilot trial was conducted in line with Consolidated Standards of Reporting Trials (CONSORT) Guidelines. The Ethical Committee of the Second Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine (Guangdong Provincial Hospital of Traditional Chinese Medicine; Guangdong, China) approved this study on 2 September 2020 (BF2020-182–01). The trial was registered in the Chinese Clinical Trial Registry on 12 September 2020 (ChiCTR2000038172) and started on 8 October 2020. The study purpose and procedures were explained to all participants in detail on an information sheet. Written informed consent was obtained from each participant. Participants were assigned randomly to the WDG group or placebo group at a ratio of 1:1. All patients received the ERAS protocol as their standard perioperative protocol (Table 1). This protocol was created with reference to the Chinese consensus and clinical guidelines for ERAS (2018 edition) [19] and the Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery from the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons [13]. The patients received WDG or placebo granule twice a day in addition to ERAS-based perioperative care, starting on post-operative Day 1 until post-operative Day 3. The 3-week study period included 2 weeks of follow-up.

### Participants

A total of 75 patients were assessed for eligibility in the study. The inclusion criteria were as follows: (i) patients who had undergone laparoscopic intestinal resection; (ii) age $\geq$18 years; (iii) duration of surgical procedure: 2.5–4.5 h; (iv) duration of anesthesia: 3–5 h; (v) type of traditional Chinese medicine syndrome: Qi deficiency and Qi stagnation; and (vi) willingness to provide written informed consent. Exclusion criteria were as follows: (i) advanced malignant tumor cachexia and extreme weakness; (ii) malignant tumors necessitating extended radical surgery or enterostomy; (iii) cardiovascular, liver, kidney, brain, lung, or other serious complications occurring before taking the study medication; (iv) poorly controlled hypertension or diabetes mellitus; (v) mental illness; (vi) allergy to study intervention; (vii) pregnant or breast-feeding women; (viii) severe malnutrition (serum albumin $<$21 g/L, pre-albumin $<$0.1 g/L); (ix) repeated abdominal surgery and severe intestinal adhesions;

**Table 1.** Perioperative study protocol[a]

| No. | Core project | Measures |
|---|---|---|
| Preoperative interventions | | |
| 1 | Education | Introduce the anesthesia, surgery, and post-operative treatment, and gain the understanding and cooperation of patients and their families |
| 2 | Food and drink | Can drink clear fluids until 2 h before anesthesia; must fast for 6 h before surgery |
| Perioperative interventions | | |
| 1 | Antibiotics | Preventive intravenous infusion of antibiotics 30–60 min before surgery |
| 2 | Anesthesia | Short-acting sedatives, short-acting opioid analgesics, and muscle relaxants are the first choice for general anesthesia |
| 3 | Surgery | Laparoscopic surgery |
| 4 | Nasogastric tubes | Not routinely used |
| 5 | Fluid management | Intraoperative monitoring; goal-directed fluid therapy for high-risk patients |
| 6 | Intra-abdominal drains | Avoided as much as possible |
| 7 | Urinary catheters | Removed within 24 h of elective colonic or upper rectal resection; removed within 48 h of mid-rectal/lower rectal resections |
| Post-operative interventions | | |
| 1 | Analgesia | Adopt multimodal analgesia program and avoid or reduce the use of opioids |
| 2 | Post-operative diet | Resumption of eating and drinking as soon as possible after 6 h after the operation |
| 3 | Mobilization | Sit out of bed on the first day after surgery; gradually increase the number of daily steps |
| 4 | Discharge | Semi-liquid diet, off intravenous fluids, pain-free when taking oral analgesics, no signs of infection, walking freely |

[a]Reference to the Chinese Consensus and Clinical Guidelines for Enhanced Recovery After Surgery (2018 edition) and the Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons.

(x) intraoperative blood loss >400 mL, and the requirement for a blood transfusion during or after surgery; (xi) need to be transferred to intensive care unit within 6 h after surgery (e.g. multiple-organ dysfunction); (xii) emergency surgery; (xiii) post-operative treatment that has a significant impact on post-operative GI function (e.g. hyperthermic intraperitoneal chemotherapy); (xiv) currently participating in other clinical trials, or having participated in another clinical study in the previous month; or (xv) patients who were considered inappropriate to participate in the study by clinical investigators. Withdrawal criteria were as follows: (i) severe complications caused by the intervention, including severe allergic reaction or serious adverse events; (ii) serious complications not caused by the intervention, such as infection or requiring a second surgery during treatment; or (iii) refusal to continue the treatment, regardless of the reason.

## Intervention

All participants took the medication (WDG or placebo) twice a day (at 9:00 and 16:00) in addition to ERAS-based perioperative care, starting on post-operative Day 1 until Day 3. Both WDG and the placebo were manufactured by the Preparation Room of Guangdong Provincial Hospital of Traditional Chinese Medicine (Guangzhou, China) according to Good Manufacturing Practices. They were packed in bags at 10 g per bag. The placebo was composed of starch with no active ingredients. Both the WDG and placebo were similar in appearance, taste and weight, and were packaged in an identical bag.

## Outcome measurements

The time to first bowel movement after surgery, in hours and minutes, was the primary outcome of the study, starting from the end of the operation to the first defecation.

The secondary outcomes were time to first flatus, LOS and GI symptoms (including post-operative nausea, vomiting, abdominal distension, and abdominal pain). Levels of ghrelin, corticotropin-releasing hormone (CRH), tumor necrosis factor (TNF), interleukin (IL)-6, superoxide dismutase (SOD), malondialdehyde (MDA), red blood cell count, hemoglobin, and serum albumin were measured preoperatively and on post-operative Days 1 and 3. The three routine tests (blood, urine, and stool), liver- and kidney-function tests, and an electrocardiogram were performed before and after treatment. During medication administration, the observer evaluated participants three times a day (07:00 to 09:00, 11:00 to 13:00, and 17:00 to 19:00). During the 2-week follow-up period, the observer evaluated participants once a week. Adverse events occurring at any time during the treatment or follow-up period were observed and recorded in detail.

## Sample size

The purpose of our trial was to demonstrate the feasibility of the study protocol and provide basic data for the design of a large-scale clinical trial. Previous research showed that chewing gum promoted the recovery of GI function after colorectal resection; the time to first bowel movement was 56.0 ± 7.5 h [20]. We hypothesized that WDG would decrease the time to first bowel movement after laparoscopic intestinal resection by 10.0 h, in which case 13 patients per group would be required to achieve 90% power at a two-sided significance level of 5% (PASS 11.0 software). Considering a 15% dropout rate, ~30 patients (15 patients in each group) would be recruited for this study.

## Randomization and double-blinding

Random numbers were generated through the website and maintained by professional statisticians. The packaging and labeling of the drug and placebo were conducted by medical staff independent of the research team. Neither the participants nor the investigators knew which participants took WDG or placebo. Blinding codes were broken only when all processes were

completed, at the request of the Human Research Ethics Committee, or if there was a serious adverse event (http://192.168.195.54:8088/randomization/portal/portalLogin).

### Statistical analyses

Data were analysed with SPSS® software version 24 (IBM, Armonk, NY, USA). A *P*-value of $<0.05$ was considered statistically significant. Results were analysed as both intention-to-treat (ITT) and per-protocol (PP). The ITT population was defined as patients who received at least one dose of the study medication and who had at least one gastrointestinal assessment. The PP population was defined as the patients who completed the treatment originally allocated. Student's *t*-tests and Mann–Whitney *U* tests were used to assess statistical significance. Intergroup differences in categorical data were analysed by using the $\chi^2$ test or Fisher's exact tests.

## Results

### Study population

The study was conducted between November 2020 and March 2021 with 30 patients selected from 75 patients undergoing laparoscopic intestinal resection (Figure 1). Two patients (one in each group) were found to have undergone extended radical surgery and two patients (one in each group) were required to undergo intraperitoneal hyperthermic perfusion on post-operative Day 1, which had an impact on the recovery of GI function. Thus, they were eliminated from the study. Three patients (two from the WDG group and one from the placebo group) did not continue taking the WDG or placebo but allowed researchers to continue to observe them. A total of 26 patients were included in the ITT analysis and the PP analysis set consisted of 23 patients. Baseline demographics and surgery characteristics were well balanced between treatment groups (Table 2).

### Efficacy and safety

The median time for the first bowel movement in the WDG group was significantly shorter than that in the placebo group (27.6 vs 50.1 h, $P < 0.001$). The median time to first flatus in the WDG group was also shorter than that in the placebo group, but the difference was not statistically significant (22.9 vs 25.1 h, $P > 0.05$). The median time for the LOS in the two groups was the same but the mean LOS in the WDG group was slightly shorter than that in the placebo group (4.6 vs 5.0 days, $P > 0.05$). No adverse events occurred in any patients and there were no obvious abnormalities in the liver- and kidney-function tests or electrocardiograms. The morbidities of post-operative nausea,

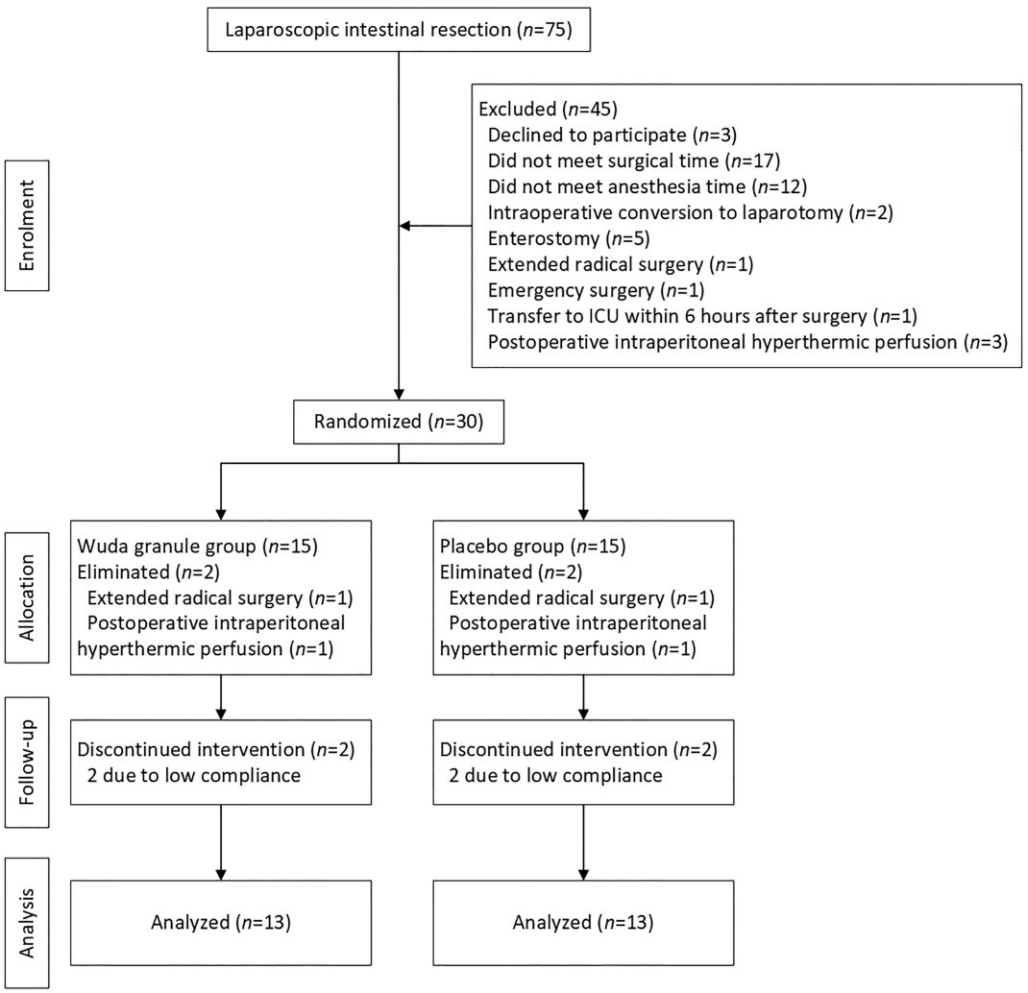


**Figure 1.** Trial flow diagram.

**Table 2.** Baseline demographics and surgical characteristics of study patients

| Characteristic | Wuda granule ($n = 13$) | Placebo ($n = 13$) | P |
|---|---|---|---|
| Median age (range), years[a] | 59 (47–74) | 62 (38–81) | 0.506 |
| Gender, $n$[b] | | | >0.999 |
| Male | 7 | 6 | |
| Female | 6 | 7 | |
| Tumors, $n$[b] | | | 0.827 |
| Ascending colon | 2 | 2 | |
| Transverse colon | 3 | 1 | |
| Descending colon | 1 | 1 | |
| Sigmoid colon | 3 | 6 | |
| Rectum | 4 | 3 | |
| History of abdominal surgery, $n$[b] | | | >0.999 |
| Yes | 2 | 3 | |
| No | 11 | 10 | |
| Surgery time, $n$[b] | | | >0.999 |
| 2.5–3.5 h | 12 | 12 | |
| 3.5–4.5 h | 1 | 1 | |
| Anesthesia time, $n$[b] | | | 0.411 |
| 3.0–4.0 h | 3 | 6 | |
| 4.0–5.0 h | 10 | 7 | |

[a]Mann–Whitney $U$ test.
[b]Fisher's exact test.

**Table 3.** Outcome variables in patients receiving Wuda granule after laparoscopic intestinal resection compared with placebo

| Variable | Intention-to-treat population | | P | Per-protocol population | | P |
|---|---|---|---|---|---|---|
| | Wuda granule ($n = 13$) | Placebo ($n = 13$) | | Wuda granule ($n = 11$) | Placebo ($n = 12$) | |
| Post-operative time to first bowel movement (h)[a] | | | 0.002* | | | 0.002* |
| Median (range) | 27.6 (20.7–49.8) | 50.1 (26.8–67.8) | | 27.4 (20.7–49.8) | 50.1 (26.8–67.8) | |
| Mean (SD) | 31.7 ± 10.2 | 48.3 ± 14.0 | | 29.6 ± 9.6 | 48.3 ± 14.0 | |
| Post-operative time to first flatus (h)[a] | | | 0.479 | | | 0.379 |
| Median (range) | 22.9 (16.2–45.9) | 25.1 (16.8–49.0) | | 22.7 (16.2–39.1) | 23.9 (16.8–49.0) | |
| Mean (SD) | 26.3 ± 9.3 | 30.0 ± 11.3 | | 23.4 ± 6.5 | 29.2 ± 11.4 | |
| Length of hospital stay (days)[a] | | | 0.311 | | | 0.169 |
| Median (range) | 5 (4–6) | 5 (4–6) | | 5 (4–5) | 5 (4–6) | |
| Mean (SD) | 4.6 ± 0.6 | 5.0 ± 0.9 | | 4.6 ± 0.5 | 5.1 ± 0.9 | |
| Number of patients[b] | | | | | | |
| Nausea | 0 | 1 | >0.999 | 0 | 1 | >0.999 |
| Vomiting | 0 | 1 | >0.999 | 0 | 0 | >0.999 |
| Abdominal distension | 1 | 3 | 0.593 | 1 | 3 | 0.593 |
| Abdominal pain | 1 | 2 | >0.999 | 1 | 2 | >0.999 |

[a]Mann–Whitney $U$ test.
[b]Fisher's exact test.
*P-value < 0.05 was considered statistically significant. The intention-to-treat population was defined as patients who received at least one dose of study medication and who had at least one gastrointestinal assessment. The per-protocol population was defined as only those patients who completed the treatment originally allocated.

vomiting, abdominal distension, and abdominal pain were similar in the two groups (Table 3).

## Gastrointestinal hormone levels

The ghrelin levels preoperatively and on post-operative Day 1 in the WDG group were lower than those in the placebo group, but the differences were not statistically significant (both $P > 0.05$). However, on post-operative Day 3, the ghrelin level in the WDG group was higher than that in the placebo group, although this was not statistically significant ($P > 0.05$). CRH levels were similar in the two groups preoperatively and on post-operative Day 1 ($P > 0.05$), while on post-operative Day 3, the CRH level in the WDG group was significantly higher than that in the placebo group ($P < 0.05$) (Table 4).

## Inflammation

Preoperative TNF and IL-6 levels in the WDG group were lower than those in the placebo group; however, they were higher than those in the placebo group on the first day after the operation but this was not a statistically significant difference ($P > 0.05$). On the third day after the operation, the TNF level in the WDG group decreased and was similar to that in the placebo group ($P > 0.05$) and the IL-6 level in the WDG group was lower than that in the placebo group ($P > 0.05$) (Table 4).

**Table 4.** Laboratory results in study patients

| Variable | Time | Wuda granule ($n = 13$) | Placebo ($n = 13$) | P[a] |
|---|---|---|---|---|
| Ghrelin (pg/mL) | Preoperatively | 122.1 ± 73.1 | 139.0 ± 48.4 | 0.315 |
| | Post-operative Day 1 | 105.4 ± 65.2 | 119.8 ± 100.8 | 0.928 |
| | Post-operative Day 3 | 137.9 ± 81.5 | 127.9 ± 39.6 | 0.965 |
| CRH (ng/mL) | Preoperatively | 2.2 ± 1.4 | 2.1 ± 0.6 | 0.143 |
| | Post-operative Day 1 | 1.9 ± 0.7 | 1.9 ± 0.9 | 0.449 |
| | Post-operative Day 3 | 1.8 ± 0.4 | 1.4 ± 0.3 | 0.027* |
| TNF (pg/mL) | Preoperatively | 5.1 ± 0.9 | 6.3 ± 1.5 | 0.181 |
| | Post-operative Day 1 | 6.7 ± 1.4 | 5.6 ± 1.1 | 0.113 |
| | Post-operative Day 3 | 5.7 ± 1.0 | 5.5 ± 1.0 | 0.408 |
| IL-6 (pg/mL) | Preoperatively | 3.8 ± 1.6 | 5.0 ± 3.5 | 0.886 |
| | Post-operative Day 1 | 72.3 ± 63.9 | 50.7 ± 48.1 | 0.362 |
| | Post-operative Day 3 | 8.7 ± 4.7 | 10.3 ± 14.0 | 0.468 |
| SOD (U/mL) | Preoperatively | 165.0 ± 15.8 | 167.7 ± 20.4 | 0.608 |
| | Post-operative Day 1 | 141.1 ± 15.4 | 151.6 ± 14.6 | 0.044* |
| | Post-operative Day 3 | 133.2 ± 13.4 | 132.5 ± 19.2 | 0.684 |
| MDA (ng/mL) | Preoperatively | 384.6 ± 106.7 | 396.3 ± 74.7 | 0.820 |
| | Post-operative Day 1 | 371.1 ± 74.8 | 351.6 ± 73.5 | 0.755 |
| | Post-operative Day 3 | 368.7 ± 50.2 | 400.7 ± 84.7 | 0.460 |
| RBC ($10^{12}$/L) | Preoperatively | 4.3 ± 0.6 | 4.3 ± 0.5 | 0.981 |
| | Post-operative Day 1 | 3.9 ± 0.4 | 3.9 ± 0.5 | 0.809 |
| | Post-operative Day 3 | 4.0 ± 0.5 | 3.8 ± 0.4 | 0.408 |
| Hb (g/L) | Preoperatively | 117.0 ± 22.3 | 117.5 ± 23.8 | 0.583 |
| | Post-operative Day 1 | 99.6 ± 31.1 | 109.5 ± 16.9 | 0.403 |
| | Post-operative Day 3 | 106.7 ± 18.4 | 102.5 ± 13.6 | 0.633 |
| ALB (g/L) | Preoperatively | 44.0 ± 4.3 | 43.2 ± 3.9 | 0.793 |
| | Post-operative Day 1 | 34.0 ± 3.4 | 35.6 ± 3.0 | 0.274 |
| | Post-operative Day 3 | 37.8 ± 3.4 | 35.8 ± 3.8 | 0.237 |

[a]Mann–Whitney *U* test.
*P-value $< 0.05$ was considered statistically significant.
CRH, corticotropin-releasing hormone; TNF, tumor necrosis factor; IL-6, interleukin-6; SOD, superoxide dismutase; MDA, malondialdehyde; RBC, red blood cell count; Hb, hemoglobin; ALB, albumin.

### Oxidative stress

Although blood levels of SOD were lower in the WDG group than in the placebo group preoperatively ($P > 0.05$) and on post-operative Day 1 ($P < 0.05$), they were higher than those in the placebo group on post-operative Day 3 but there was no statistically significant difference ($P > 0.05$). In contrast, MDA levels were lower preoperatively but higher on post-operative Day 1 in the WDG group than in the placebo group. However, on post-operative Day 3, the MDA level in the WDG group was lower than that in the placebo group, although this was not statistically significant ($P > 0.05$) (Table 4).

### Other factors

Although the levels of red blood cell count, hemoglobin, and albumin in the WDG group were similar to or slightly lower than those in the placebo group on post-operative Day 1, they were all slightly higher on post-operative Day 3 but there were no statistically significant differences (all $P > 0.05$) (Table 4).

## Discussion

In this pilot study on the efficacy of WDG after laparoscopic intestinal resection in the setting of ERAS-based perioperative care, the time to first flatus and the time to first bowel movement for patients in the WDG group were shorter than those in the placebo group and the difference in the time to first bowel movement was statistically significant. The morbidities of post-operative nausea, vomiting, abdominal distension, and abdominal pain were similar in the two groups. No adverse events occurred in any patients.

The etiology of POI is complex and the main internal influencing factors are surgical stress (i.e. physical manipulation of the intestine), secretion of inflammatory mediators and endogenous opioids in the GI tract, and changes in hormone levels as well as electrolytes and fluid balance [21–24]. Ghrelin is a brain–gut peptide secreted by the gastric mucosa. It can regulate growth hormone secretion and has an effect on gastrointestinal motility via the vagus nerve and enteric nervous system. CRH is a physiologic brain–gut peptide. It also plays an important role in gastrointestinal motility. Although CRH can delay gastric emptying, it can also promote colonic motility. Previous research showed that WDG could effectively promote the recovery of GI function after gynecologic surgery, which may be related to promoting ghrelin recovery and reducing the post-operative CRH secretion [17]. This pilot study showed that on post-operative Day 3, ghrelin levels in the WDG group were higher than those in the placebo group. These results are consistent with those of previous studies. However, CRH levels in the WDG group were also higher than in the placebo group, which is contrary to the results of previous research. This may be related to the fact that we only included patients who underwent intestinal resection patients, the small sample size, or other factors.

GI motility disorder is closely related to inflammation. Preventing inflammation-related intestinal wall damage is considered a promising treatment strategy for improving post-operative GI motility disorders [25]. Previous animal experiments

showed that WDG could ameliorate impaired GI motility in a POI rat model by inhibiting the mesenteric inflammatory response [26]. Our study results showed that the level of TNF in the WDG group was higher than that in the placebo group on the first post-operative day but they were similar on the third day after surgery, which indicates that the TNF level greatly decreased in the WDG group. In addition, compared with the first day after surgery, the level of IL-6 in the WDG group was significantly decreased on post-operative Day 3 and was also greatly decreased compared with that in the placebo group, although this trend did not reach statistical significance.

GI dysfunction is mainly caused by the destruction of the GI mucosal barrier and intestinal mucosal hypoperfusion, cytokine action, and oxygen free-radical damage are the three major injury factors in the intestinal mucosa, with oxygen free-radical damage being the most important. SOD is an important antioxidant enzyme that can remove excess free radicals and antagonize the oxidative stress response. MDA is a key indicator reflecting the severity of free-radical damage in the body. One study found that reducing oxidative stress could increase ghrelin expression in the gastric tissues of rats with gastroparesis [27]. The present study found that WDG has the potential to enhance the SOD level and promote a decline in MDA.

Because of the impact of the disease, the nutritional status of tumor patients was reduced to varying degrees, especially in cases of GI tumors. Moreover, surgical trauma often causes malnutrition, which significantly increases the risk of post-operative death and complications. Although the levels of red blood cell count, hemoglobin, and albumin in the WDG group were lower than those in the placebo group on post-operative Day 1, they were all higher on post-operative Day 3. These results indicate that WDG may improve the patients' nutritional status after laparoscopic intestinal resection.

Our study had several limitations. First, this was a pilot study in laparoscopic intestinal resection; because the purpose of the trial was to demonstrate the feasibility of the study protocol and accumulate clinical data, the sample size was small. Second, surgery and anesthesia are two factors that affect the recovery of GI function after surgery. Considering the small sample size, we only included patients who underwent laparoscopic intestinal resection with an operative time of 2.5–4.5 h and anesthesia time of 3.0–5.0 h. Because of these limitations, only patients with colorectal tumors and those undergoing colorectal resection were included. Third, van Bree *et al.* [28] reported that the time to tolerate solid food and time to first bowel movement are more indicative of the recovery of GI function than the time to first flatus and recommended that those times should be considered as primary outcome measures in future clinical trials of POI. However, the clinicians in our hospital did not reach a consensus on giving the patients solid food after surgery to assess the time to tolerate the solid food and patients often refuse to advance to solid foods too early; therefore, only the time to first bowel movement was used as the primary outcome measure. Fourth, although the mean LOS was slightly shorter in the WDG group than in the placebo group (4.6 vs 5.0 days), the median time for LOS in the two groups was similar in this pilot study. Last, alvimopan has not been introduced in China and cannot be introduced into this study; meanwhile, this study was a randomized double-blind trial and therefore chewing gum could not be used as a positive control group. Despite these limitations, the results of this study will provide basic data for the design of a large-scale clinical trial evaluating WDG efficacy and safety in speeding up the recovery of GI function after laparoscopic intestinal resection.

## Conclusions

WDG could promote the rapid recovery of GI function after laparoscopic intestinal resection in the setting of ERAS-based perioperative care, which may be related to regulating GI hormone levels, reducing inflammation and oxidative stress, and improving nutritional status. The morbidity of post-operative nausea, vomiting, abdominal distension, and abdominal pain was similar in the two groups and no adverse events occurred in any patients, which indicated that WDG administration was safe.

## Authors' Contributions

Z.C. designed the study. L.C., J.W., W.W., and D.D. assisted in designing the study. H.Z. and Y.W. collected the case and completed the database. H.Z. and W.O. analysed data. L.C. and Q.C. were responsible for the quality control of the study implementation process, including data verification. H.Z. drafted the manuscript. L.C. and W.W. were responsible for revising the manuscript. Z.C. was responsible for the final review.

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## Conflict of Interest

None declared.

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