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Preclosure Distal-Limb Nutritive Stimulation Before Ileostomy Closure: A Single-Center Feasibility Study of Short-Term Gastrointestinal Outcomes

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Abstract

Background

Postoperative diarrhea after ileostomy closure may reflect impaired adaptation of the previously diverted bowel and may be clinically relevant when mucosal injury raises concerns about barrier dysfunction and systemic infection. This study evaluated the feasibility, tolerability, and short-term outcomes of continuous preclosure administration of glutamine, fiber, and oligosaccharide formulation to the distal limb.

Methods

This single-center retrospective observational study included patients who underwent ileostomy closure after left-sided colorectal cancer surgery between January 2014 and December 2023. The primary analysis included 126 patients who received continuous distal-limb administration for at least 4 days before closure. The primary outcome was 30-day postoperative gastrointestinal events, defined as frequent watery stools without *Clostridioides difficile* infection, *Clostridioides difficile*-associated diarrhea, or ileus. Exploratory analyses were performed to identify candidate variables for future risk stratification.

Results

The median administration period was 7 days. Thirty-day gastrointestinal events occurred in 12 patients (9.5%; 95% confidence interval, 5.5–15.9). Frequent watery stools without *Clostridioides difficile* infection, *Clostridioides difficile*-associated diarrhea, and ileus each occurred in four patients (3.2%; 1.2–7.9). No Clavien–Dindo grade III or higher complications, postoperative sepsis, or serious intervention-related adverse events were observed. Body mass index ≥ 25 kg/m² showed a possible association with postoperative frequent stools or diarrhea.

Conclusion

Continuous preclosure distal-limb nutritive stimulation was feasible and tolerable in selected patients, with low observed rates of short-term gastrointestinal events and no postoperative sepsis. These findings support prospective comparative studies to evaluate whether this strategy improves bowel adaptation after ileostomy closure and to identify patients most likely to benefit.

Introduction

Gastrointestinal problems related to a previously diverted bowel, including diversion colitis, postoperative diarrhea, and ileus, may become clinically relevant after stoma closure when fecal flow is restored. Diversion colitis may reflect mucosal inflammation and impaired barrier function in the

defunctioned bowel, and severe mucosal injury may theoretically raise concerns about bacterial translocation or systemic infectious complications after restoration of intestinal continuity. Therefore, postoperative diarrhea or frequent watery stools after stoma closure may represent clinically relevant manifestations of impaired bowel adaptation rather than minor symptoms alone. These complications can prolong hospitalization or lead to readmission, highlighting their importance in perioperative management. In the diverted bowel, a reduced supply of short-chain fatty acids (SCFAs), mucosal atrophy, and alterations in the intestinal microbiota are known to contribute to the development of diversion colitis [1, 2].

SCFA irrigation and preclosure stimulation of the defunctioned bowel have been investigated for the treatment of diversion colitis and for postoperative bowel recovery. Although SCFA irrigation has been reported to improve symptoms and endoscopic inflammation [3], the efficacy of nonsurgical treatments for diversion colitis remains inconsistent [2]. Similarly, preclosure bowel stimulation may facilitate postoperative bowel recovery; however, the available evidence is limited [4].

Therefore, evidence regarding standardized nutritional interventions for the distal limb before stoma closure in routine practice remains limited. GFO®, a formulation containing glutamine, fiber, and oligosaccharide, may help maintain intestinal mucosal integrity, provide substrates for SCFA production, and modulate the intestinal environment [5, 6].

In this study, we retrospectively evaluated patients who received continuous preclosure administration of GFO® into the distal limb before temporary ileostomy closure after left-sided colorectal cancer surgery. This intervention was intended to provide nutritive stimulation to the diverted distal bowel before restoration of fecal flow. The aim of this study was to describe the feasibility, tolerability, and short-term postoperative outcomes of this standardized protocol, including the incidence of noninfectious frequent watery stools, *Clostridioides difficile* (*C. difficile*)-associated diarrhea, and ileus. This study was designed as a hypothesis-generating, single-arm evaluation rather than a comparative efficacy study.

Methods

Study design and participants

This single-center, retrospective observational study was conducted at Asahikawa Medical University, Japan. We reviewed patients who underwent ileostomy closure between January 2014 and December 2023 and identified those with temporary ileostomies created after resection of left-sided colorectal cancer. Patients who developed anastomotic leakage after the primary colorectal procedure were excluded. The primary analysis included patients who received GFO® (glutamine, fiber, and oligosaccharide formulation) into the distal limb for at least 4 days before ileostomy closure. The GFO group was considered the protocol-completion cohort. Patients who did not receive GFO® or received it for fewer than 4 days were described separately to assess the feasibility and limitations of implementing

the protocol (Fig. 1). A minimum duration of 4 days was chosen because it represented the shortest duration considered sufficient to complete the institutional preclosure administration protocol.

The endoscopic findings of the distal limb before ileostomy closure were obtained from routine endoscopy reports. These findings were recorded descriptively as part of usual clinical practice and were not graded using a standardized endoscopic severity score. Therefore, endoscopic variables were only evaluated as exploratory descriptors of the diverted bowel condition.

Intervention

In principle, patients were admitted approximately 1 week before ileostomy closure. An enteral feeding tube (Kangaroo™ New Enteral Feeding Tube, 6.5 Fr) was inserted through the distal limb of the stoma under fluoroscopic guidance. The tube tip was advanced into the right colon whenever feasible or positioned as far distally as possible within the distal limb. GFO® solution was then administered continuously through the tube (Fig. 2). On the first day of administration, one GFO® stick was dissolved in 150 mL water and infused at a rate of 30 mL/h. From the second day of administration until the day before surgery, two GFO® sticks were dissolved in 150 mL water and infused at the same rate.

The GFO® formulation used in this study (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) is a powdered beverage containing glutamine, fiber, and oligosaccharide. Each 10-g stick contained 3.0 g of glutamine, 3.0 g of dietary fiber as partially hydrolyzed guar gum, 1.45 g of fructooligosaccharide, and 30 kcal. Intervention-related adverse events including tube-related complications, aspiration, abdominal pain requiring discontinuation, and leakage-related skin complications were assessed using the medical records.

Ileostomy closure was performed via resection and reconstruction of the small bowel segment containing the stoma. Reconstruction was generally performed via functional end-to-end anastomosis; hand-sewn anastomosis was performed in two patients.

Outcomes

The primary outcome was 30-day postoperative gastrointestinal events, defined as frequent watery stools without *C. difficile* infection, *C. difficile*-associated diarrhea, or ileus.

The diagnostic criteria for each event were as follows. Testing for *C. difficile* was performed when patients developed frequent watery stools or clinically suspected infectious diarrhea after ileostomy closure. Routine screening for *C. difficile* infection was not performed in asymptomatic patients. Frequent watery stools without *C. difficile* infection were defined as more than five watery stools per day occurring on or after postoperative day 3, without fever or clinically relevant inflammatory findings suggestive of infection and with a negative *C. difficile* test result. This threshold was based on institutional clinical criteria used to identify patients requiring additional evaluation or treatment for

postoperative diarrhea. Postoperative day 3 was selected to avoid misclassification of transient bowel hyperactivity immediately after the restoration of intestinal continuity. *C. difficile*-associated diarrhea was defined as diarrhea symptoms, namely more than five watery stools per day from postoperative day 3 onward, with a positive *C. difficile* test result. Ileus was defined as small bowel dilatation on imaging that required nasogastric decompression or cessation of oral intake for at least 48 h.

Secondary outcomes included the incidence of each component event, surgical site infection, urinary tract infection, bacteremia, sepsis, postoperative nausea and vomiting, Clavien–Dindo classification, operative time, and intraoperative blood loss. The observation period was 30 days after ileostomy closure. Outcomes were assessed from the medical records by at least two surgeons, and disagreements were resolved through discussion.

The primary outcome was determined on a patient-specific basis. Component events were mutually exclusive in this cohort.

Statistical analysis

Primary and secondary outcomes are expressed as proportions with 95% confidence intervals (CIs) calculated using the Wilson method. Continuous variables are presented as medians with interquartile ranges. For exploratory analyses of postoperative frequent stools or diarrhea, Fisher's exact test was used for categorical variables and the Mann–Whitney U test for continuous variables. Clinically relevant and preoperatively available variables were selected as candidate factors for future risk stratification: age ≥ 65 years, male sex, body mass index (BMI) ≥ 25 kg/m², albumin < 4.0 g/dL, interval from stoma creation to closure ≥ 6 months, and adjuvant chemotherapy. BMI ≥ 25 kg/m² was selected as a clinically interpretable threshold for overweight or obesity in Japanese patients and was not determined from the present dataset. Exploratory receiver operating characteristic curve analysis was performed for BMI. Because of the small number of events, these analyses were descriptive, not adjusted for multiple comparisons, and not intended to identify independent risk factors, develop a prediction model, or establish a validated cutoff value. For the non-GFO group (n = 14), patient characteristics and crude event rates are described in the supplementary table. No statistical comparison with the GFO group was performed, and these data were considered hypothesis-generating. Statistical analyses were performed using EZR version 1.64 [7]. Statistical significance was set at $P < 0.05$. Missing data were excluded from the denominator of each variable.

Results

Patient characteristics

Characteristics of the 126 patients in the GFO group are shown in Table 1. The median age was 67.0 years [interquartile range (IQR), 59.0–73.0], and 87 patients (69.0%) were men. The median BMI was 21.4 kg/m² [19.6–24.2], and the median skeletal muscle index was 6.4 cm²/m² [5.8–7.5]. The American

Society of Anesthesiologists physical status grades 1, 2, and 3 were observed in 9 (7.1%), 111 (88.1%), and 6 (4.8%) patients, respectively.

Table 1
Patient characteristics and perioperative outcomes of the GFO group (n = 126)

Variable	Value
Age, years	67.0 [59.0–73.0]
Sex, men	87 (69.0)
BMI, kg/m²	21.4 [19.6–24.2]
SMI, cm²/m²	6.4 [5.8–7.5]
ASA-PS	
Grade 1	9 (7.1)
Grade 2	111 (88.1)
Grade 3	6 (4.8)
Albumin, g/dL	4.2 [3.9–4.4]
Transferrin, mg/dL	277.1 [237.4–325.1]
Transthyretin, mg/dL	26.4 [22.4–29.6]
mGPS	
0	115 (91.3)
1	8 (6.3)
2	3 (2.4)
CONUT score	1 [0–2]
PNI	49.5 [45.9–53.2]
NLR	2.1 [1.7–2.8]
PLR	140.9 [104.0–176.9]
Index colorectal procedure	
LAR	123 (97.6)

Values are presented as medians [interquartile ranges] or n (%).

† Endoscopic findings were not mutually exclusive.

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CONUT, controlling nutritional status; GFO, glutamine, fiber, and oligosaccharide; IQR, interquartile range; LAR, low anterior resection; mGPS, modified Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SC, sigmoid colectomy; SMI, skeletal muscle index; uLAR, ultralow anterior resection.

Variable	Value
SC	2 (1.6)
uLAR	1 (0.8)
Adjuvant chemotherapy	71 (56.3)
Endoscopic findings before stoma closure[†]	
Inflammation	21 (16.7)
Atrophy	15 (11.9)
Stenosis	14 (11.1)
Days of GFO administration	7 [6–7]
Time from stoma creation to closure, days	195 [117–252]
Operative time, min	99 [79–129]
Operative blood loss, mL	26 [14–50.5]
Postoperative hospital stay, days	10 [8–12]
Values are presented as medians [interquartile ranges] or n (%).	
[†] Endoscopic findings were not mutually exclusive.	
Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; CONUT, controlling nutritional status; GFO, glutamine, fiber, and oligosaccharide; IQR, interquartile range; LAR, low anterior resection; mGPS, modified Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SC, sigmoid colectomy; SMI, skeletal muscle index; uLAR, ultralow anterior resection.	

Regarding nutritional and inflammatory markers, the median albumin level was 4.2 g/dL [3.9–4.4], the median transferrin level was 277.1 mg/dL [237.4–325.1], and the median transthyretin level was 26.4 mg/dL [22.4–29.6]. The modified Glasgow prognostic scores were 0, 1, and 2 in 115 (91.3%), 8 (6.3%), and 3 (2.4%) patients, respectively. The median CONUT score was 1 [0–2], the median prognostic nutritional index was 49.5 [45.9–53.2], the median neutrophil-to-lymphocyte ratio was 2.1 [1.7–2.8], and the median platelet-to-lymphocyte ratio was 140.9 [104.0–176.9].

The index colorectal procedure was low anterior resection in 123 patients (97.6%), sigmoid colectomy in two (1.6%), and ultralow anterior resection in one (0.8%). Chemotherapy was administered to 71 patients (56.3%). The endoscopic findings in the distal limb included inflammation in 21 patients (16.7%), atrophy in 15 (11.9%), and stenosis in 14 (11.1%). The median duration of GFO administration was 7 days [range, 6–7 days], and the median interval from stoma creation to closure was 195 days [range, 117–252 days]. The median operative time was 99 min [range, 79–129 min], median intraoperative blood loss was 26 mL [range, 14–50.5 mL], and median postoperative hospital stay was 10 days [8–12].

Thirty-day postoperative outcomes

The 30-day postoperative outcomes of the GFO group are shown in Table 2. The primary outcome, 30-day gastrointestinal events, occurred in 12 patients (9.5%; Wilson 95% confidence interval, 5.5–15.9). The components were frequent watery stools without *C. difficile* infection in four patients (3.2%; 1.2–7.9%), *C. difficile*-associated diarrhea in four patients (3.2%; 1.2–7.9%), and ileus in four patients (3.2%; 1.2–7.9%). Other postoperative complications included surgical site infection in three patients (2.4%; 0.8–6.8%), urinary tract infection in two (1.6%; 0.4–5.6%), postoperative nausea and vomiting in one (0.8%; 0.1–4.4%), and bacteremia in one (0.8%; 0.1–4.4%). According to the Clavien–Dindo classification, grade I and II complications occurred in five (4.0%) and 14 (11.1%) patients, respectively. No Clavien–Dindo grade III or higher complications, postoperative sepsis, or serious intervention-related adverse events were observed.

Table 2
Thirty-day postoperative outcomes in the GFO group (n = 126)

Outcome	**n (%) [Wilson 95%CI]**
Frequent stools or diarrhea without *C. difficile* infection	4 (3.2) [1.2–7.9]
C. difficile infection-associated diarrhea	4 (3.2) [1.2–7.9]
Ileus	4 (3.2) [1.2–7.9]
SSI	3 (2.4) [0.8–6.8]
UTI	2 (1.6) [0.4–5.6]
PONV	1 (0.8) [0.1–4.4]
Bacteremia	1 (0.8) [0.1–4.4]
Sepsis	0 (0) [0.0–3.0]
Clavien–Dindo grade	
Grade I	5 (4.0) [1.7–9.0]
Grade II	14 (11.1) [6.8–17.8]
Grade ≥ III	0 (0) [0.0–3.0]
The primary outcome was determined on a patient-specific basis. Component events were mutually exclusive in this cohort.	
Values are presented as n (%) [Wilson 95% confidence interval].	
The Clavien–Dindo grade indicates the highest grade per patient.	
Abbreviations: *C. difficile*, *Clostridioides difficile*; SSI, surgical site infection; UTI, urinary tract infection; PONV, postoperative nausea and vomiting; CI, confidence interval.	

Exploratory comparison according to postoperative frequent stools or diarrhea

An exploratory comparison based on the presence or absence of postoperative frequent stools or diarrhea is shown in Supplementary Table S1. Frequent stools or diarrhea occurred in eight patients. Patients with frequent stools or diarrhea had longer total and postoperative hospital stays than those without these symptoms. Differences in BMI, body weight, platelet-to-lymphocyte ratio, and platelet count were also observed. *C. difficile* infection was identified in four of eight patients with frequent stools or diarrhea.

An exploratory candidate-factor analysis for postoperative frequent stools or diarrhea is shown in Table 3. Among the predefined dichotomized variables, BMI ≥ 25 kg/m² showed a possible association with a higher incidence of postoperative frequent stools or diarrhea than BMI < 25 kg/m² (5/26 [19.2%] vs. 3/100 [3.0%], P = 0.009). Age ≥ 65 years, male sex, albumin < 4.0 g/dL, interval from stoma creation to closure ≥ 6 months, and adjuvant chemotherapy were not associated with postoperative frequent stools or diarrhea. In a supplementary exploratory receiver operating characteristic curve (ROC) analysis, BMI showed an area under the curve of 0.743, although the 95% confidence interval was wide (0.528–0.957).

Table 3
Exploratory candidate-factor analysis for postoperative frequent stools or diarrhea

Variable	**Factor-positive**	**Factor-negative**	***P value***
Candidate factor			
Age at stoma closure ≥ 65 years	7/81 (8.6)	1/45 (2.2)	0.257
Sex, men	7/87 (8.0)	1/39 (2.6)	0.433
Chemotherapy	5/71 (7.0)	3/55 (5.5)	1.000
BMI before stoma closure ≥ 25 kg/m²	5/26 (19.2)	3/100 (3.0)	**0.009**
Albumin before stoma closure < 4.0 g/dL	1/36 (2.8)	7/90 (7.8)	0.438
Interval from stoma creation to closure ≥ 6 months	4/67 (6.0)	4/59 (6.8)	1.000

Values are presented as n/N (%). P values were calculated using Fisher's exact test for categorical variables. Candidate factors were selected because they were clinically relevant and available prior to ileostomy closure. These analyses were performed only for exploratory purposes and were not intended to identify independent risk factors or develop a prediction model. No adjustments were performed for multiple comparisons.

Abbreviations: BMI, body mass index.

Exploratory description of the non-GFO group

The characteristics and crude postoperative event rates of the 14 patients in the non-GFO group are shown in Supplementary Table S2. GFO® was not administered or was administered for fewer than 4 days because of stoma prolapse in five patients, small bowel obstruction in two, stoma obstruction in one, and unknown reasons in six. Within 30 days after surgery, frequent watery stools without *C. difficile* infection occurred in three patients, and *C. difficile*-associated diarrhea, ileus, and surgical site infection each occurred in one patient. No Clavien–Dindo grade III or higher complications were observed. Because the number of patients was limited, and the reasons for non-administration or incomplete administration were closely related to stoma-related complications or bowel obstruction, this group was not considered an appropriate comparator. Therefore, no statistical comparisons were made with the GFO group.

Discussion

In this study, we evaluated the postoperative course of 126 patients who received continuous preclosure administration of GFO® into the distal limb before temporary ileostomy closure after left-sided colorectal cancer surgery. The incidence of 30-day gastrointestinal events was 9.5%, and noninfectious frequent watery stools occurred in only 3.2% of patients. In addition, *C. difficile*-associated diarrhea and ileus each occurred in 3.2% of the patients, and no Clavien–Dindo grade III or higher complications were observed. These findings indicate that the standardized protocol is feasible and tolerable in selected patients. However, as this was a retrospective single-arm study without an appropriate comparator, these results should not be interpreted as evidence that GFO® administration prevents diarrhea, ileus, or diversion colitis-related symptoms.

In the diverted bowel, interruption of fecal flow can reduce the SCFA supply and induce mucosal atrophy, changes in the intestinal microbiota, and altered mucosal immunity, all of which may contribute to diversion colitis [1, 2, 8]. After stoma closure, restoration of fecal flow may impose an abrupt physiological load on the previously diverted bowel, potentially leading to frequent stools, diarrhea, enteritis, or bowel passage disturbances. From this perspective, administration of nutritional substrates into the distal limb before closure is a biologically plausible approach.

GFO® contains glutamine, fiber, and oligosaccharide. These components may support intestinal mucosal integrity, provide substrates for SCFA production, and modulate the intestinal environment [5, 6, 9, 10]. Previous clinical studies have reported the use of GFO® for mucosal injury after hematopoietic stem cell transplantation and perioperative supplementation after esophagectomy, with few severe GFO®-related adverse events [5, 11]. However, because mucosal histology, SCFA concentrations, fecal biomarkers, and gut microbiota were not assessed, the present clinical data cannot demonstrate biological effects of GFO® on the diverted bowel.

Several treatments for diversion-induced colitis, including SCFA enemas, topical medications, and bowel stimulation, have been reported; however, no standard treatment has been established [2–4]. Although

preclosure stimulation of the defunctioned bowel is theoretically attractive, the available evidence remains limited and insufficient to support routine implementation [4, 12].

Although ileostomy closure is often considered a relatively minor procedure, postoperative morbidity is not negligible. In a systematic review, Chow et al. reported an overall morbidity rate of 17.3% and a mortality rate of 0.4% after defunctioning ileostomy closure, and small bowel obstruction and wound infection were the most common complications [13]. Rubio-Perez et al. reported high morbidity after protective ileostomy closure and an association between delayed closure and increased complications, including wound infections and enteritis [14]. Skancke et al. reported that elective stoma reversal was associated with a greater incidence of postoperative *C. difficile* infection than elective colorectal resection, highlighting the importance of distinguishing infectious causes when evaluating diarrhea after stoma closure [15]. In the present study, *C. difficile*-associated diarrhea occurred in 3.2% of patients, which is broadly consistent with previously reported rates after stoma closure. Ileus occurred in 3.2% of patients, which was lower than the 7.2% rate of small bowel obstruction reported by Chow et al. [13]. This lower incidence rate may partly reflect the surgical technique used in this cohort, in which the bowel segment containing the stoma was resected and reconstructed in all patients. However, ileus is mainly related to small bowel factors such as adhesions, anastomotic edema, or impaired motility, and its pathogenesis is likely different from that of noninfectious frequent watery stools. Therefore, the low incidence of ileus should not be interpreted as a direct result of the GFO® administration.

In this study, watery stools without *C. difficile* infection, *C. difficile*-associated diarrhea, or ileus were infrequent. Diarrhea after stoma closure may reflect functional changes associated with the restoration of fecal flow, infectious causes such as *C. difficile* infection, or inflammatory changes in the previously diverted bowel. Therefore, distinguishing non-infectious frequent watery stools from infectious diarrhea is clinically important. In addition, frequent watery stools after closure may be clinically relevant because they can reflect impaired bowel adaptation and, in severe diversion-related mucosal injury, may raise concerns about barrier dysfunction and bacterial translocation. In the present cohort, no postoperative sepsis was observed and bacteremia occurred in only one patient, supporting the short-term tolerability of this protocol in selected patients. In this context, preclosure administration of GFO®, which contains substrates such as glutamine and fiber, may be biologically plausible as a nutritive stimulation strategy for the diverted bowel. The low incidence of noninfectious frequent watery stools observed in this cohort is consistent with this concept, although biological mechanisms were not directly assessed.

In the exploratory comparison, patients with postoperative frequent stools or diarrhea had longer total and postoperative hospital stays. This finding is clinically plausible because these symptoms may require fluid replacement, dietary adjustment, probiotics or antidiarrheal medications, and evaluation for *C. difficile* infection, all of which may affect discharge timing. Differences in BMI, body weight, platelet-to-lymphocyte ratio, and platelet count were also observed. However, because the number of patients with frequent stools or diarrhea was very small, these findings should be interpreted only as descriptive and hypothesis-generating.

In the exploratory candidate-factor analysis, BMI ≥ 25 kg/m² showed a possible association with postoperative frequent stools or diarrhea, whereas other clinically selected variables did not. Supplementary exploratory ROC analysis yielded an area under the curve of 0.743 for BMI, although the 95% confidence interval was wide (0.528–0.957). The reason for this association is unclear; however, previous population-based studies and a meta-analysis have reported associations between a higher BMI or obesity and diarrhea or gastrointestinal symptoms [16, 17]. In patients with diversion colitis after low anterior resection, the BMI has also been reported to be associated with the severity of diarrhea after ileostomy closure [18]. In addition, a Japanese study on loop ileostomy closure reported a BMI of 24 kg/m² as the cutoff value associated with postoperative complications [19]. Several mechanisms may explain why a higher BMI can influence bowel symptoms after stoma closure. Obesity-related low-grade inflammation, increased intestinal permeability, dysbiosis, and altered bile acid metabolism may impair mucosal barrier function and bowel adaptation after the restoration of fecal flow [20, 21]. These findings suggest that body habitus and intestinal environment may be relevant to bowel adaptation after the restoration of fecal flow. However, because this analysis was based on only eight events and was not adjusted for multiple comparisons, BMI should be regarded only as a candidate variable in future risk-stratified studies.

A potential clinical advantage of this method is that it can be performed through the distal limb of the stoma with standardized administration volumes, rates, and durations. No Clavien–Dindo grade III or higher complications were observed, suggesting that this approach may be technically feasible in selected patients. Because gastrointestinal symptoms after stoma closure can affect the quality of life and discharge timing, preparing the diverted bowel before closure may have clinical value. However, the protocol has important practical disadvantages. It requires preoperative hospitalization for approximately one week, fluoroscopic tube placement, continuous pump administration, dedicated stoma appliances, leakage-prevention techniques using an ostomy pouch and barrier paste (Fig. 3), and additional nursing care. These requirements impose non-negligible burdens on patients and healthcare resources, including the quality of life, hospital stay, and cost. Therefore, routine implementation cannot be recommended based on single-arm data alone. Future studies should optimize patient selection, the dose, duration, and delivery method of GFO® administration, and evaluate less burdensome protocols that could be implemented in an outpatient setting or during a shorter preoperative admission.

Patients who did not receive GFO® or who received it for fewer than 4 days are described in the Supplementary Table S2. However, the non-GFO group included only 14 patients, and non-administration or incomplete administration was mainly related to stoma prolapse, stoma obstruction, or small bowel obstruction, introducing substantial selection bias. Although we considered constructing an older historical control cohort, this approach was deemed inappropriate due to concerns about data reliability from paper-based records and substantial period bias. Therefore, no comparison between the GFO and non-GFO groups was performed, and the present study should be interpreted as a single-arm feasibility and tolerability study, rather than an efficacy study.

This study has certain limitations. First, it was a single-center retrospective observational study without randomization or an appropriate comparator group; therefore, selection bias and information bias could not be fully excluded, and the efficacy of GFO® in reducing diarrhea, ileus, or diversion colitis-related symptoms could not be assessed. Second, the assessment of frequent stools and diarrhea was based on medical records; standardized stool consistency measures, such as the Bristol Stool Form Scale, were not used, and *C. difficile* testing was performed based on clinical suspicion rather than routine screening. Endoscopic findings in the distal limb were also based on descriptive routine reports rather than on standardized severity scores, and most of the findings were mild. Third, the exploratory candidate factor and ROC analyses were based on only eight events and were not adjusted for multiple comparisons. Therefore, BMI should not be regarded as a validated predictor or cutoff value. Fourth, the study period extended from 2014 to 2023, and temporal changes in perioperative management, surgical techniques, discharge criteria, and management of postoperative complications may have influenced the observed outcomes. Fifth, this study did not evaluate the intestinal microbiota, SCFA concentrations, fecal biomarkers, mucosal histology, bile acid metabolism, dietary factors, or body composition; therefore, it could not directly demonstrate the biological effects of GFO® or explain the association between BMI and postoperative bowel symptoms. Sixth, the present protocol required preoperative hospitalization and continuous inpatient administration, which may limit its generalizability and cost-effectiveness. Finally, only short-term outcomes within 30 days after surgery were assessed, and their effects on long-term bowel function and quality of life remain unknown.

Conclusion

Continuous preclosure administration of GFO® into the distal limb appeared feasible and tolerable in selected patients undergoing temporary ileostomy closure after left-sided colorectal cancer surgery. Noninfectious frequent watery stools, *C. difficile*-associated diarrhea, and ileus were infrequent, and no severe morbidity was observed. However, because this was a single-arm retrospective study without direct mechanistic assessment or an appropriate comparator, these findings should be regarded as preliminary and hypothesis-generating. Further prospective studies are needed to determine whether this approach can improve postoperative bowel function and whether a less burdensome protocol can be implemented in routine practice.

Abbreviations

ASA-PS, American Society of Anesthesiologists physical status

BMI, body mass index

C. difficile, Clostridioides difficile

CI, confidence interval

CONUT, controlling nutritional status

GFO, glutamine, fiber, and oligosaccharide

IQR, interquartile range

LAR, low anterior resection

mGPS, modified Glasgow prognostic score

NLR, neutrophil-to-lymphocyte ratio

PLR, platelet-to-lymphocyte ratio

PNI, prognostic nutritional index

PONV, postoperative nausea and vomiting

ROC, receiver operating characteristic

SC, sigmoid colectomy

SCFA, short-chain fatty acid

SMI, skeletal muscle index

SSI, surgical site infection

uLAR, ultralow anterior resection

UTI, urinary tract infection

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Asahikawa Medical University (Approval No. 19228) and was conducted in accordance with the Declaration of Helsinki and its later amendments. The requirement for written informed consent was waived owing to the retrospective nature of the study, and information about the study was disclosed via an opt-out approach.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

TT and TS contributed to the study conception and design, data collection, data analysis, and drafting of the manuscript. DK, SM, HI, MaO, MiO, CT, HT, KI, KH, and HY contributed to data interpretation and critical revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain potentially identifiable clinical information, but are available from the corresponding author on reasonable request and with permission from the Institutional Review Board of Asahikawa Medical University.

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Figures

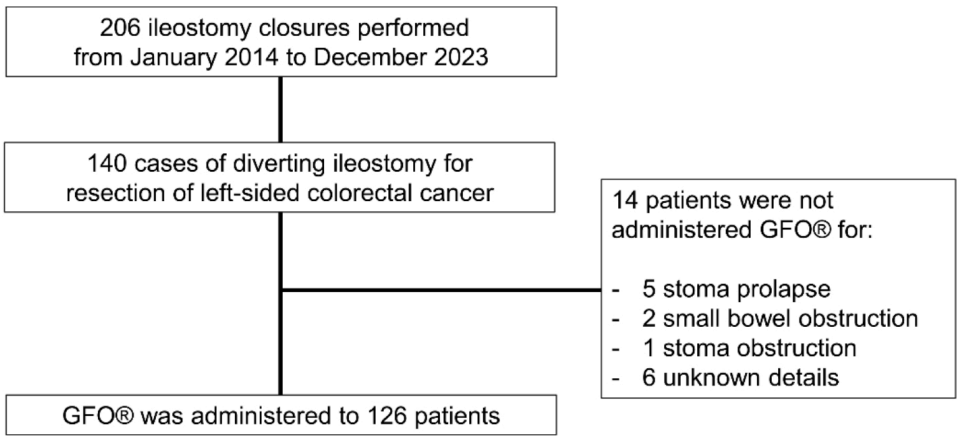

Figure 1

Patient selection flowchart

In total, 206 ileostomy closures were performed between January 2014 and December 2023. Among thesepatients, 140 had a diverting ileostomy created after the resection of left-sided colorectal cancer. GFO® was administered to 126 patients before ileostomy closure. Fourteen patients did not receive GFO® because of stoma prolapse, small bowel obstruction, stoma obstruction, or unknown reasons.



Figure 2

Administration of GFO® solution into the distal limb before ileostomy closure

(a) An enteral tube was inserted through the distal limb of the ileostomy. (b) After tube placement, the tube was connected to the infusion line and managed with an ostomy pouch. (c) GFO® solution was continuously administered inthe ward viaan infusion pump before ileostomy closure.

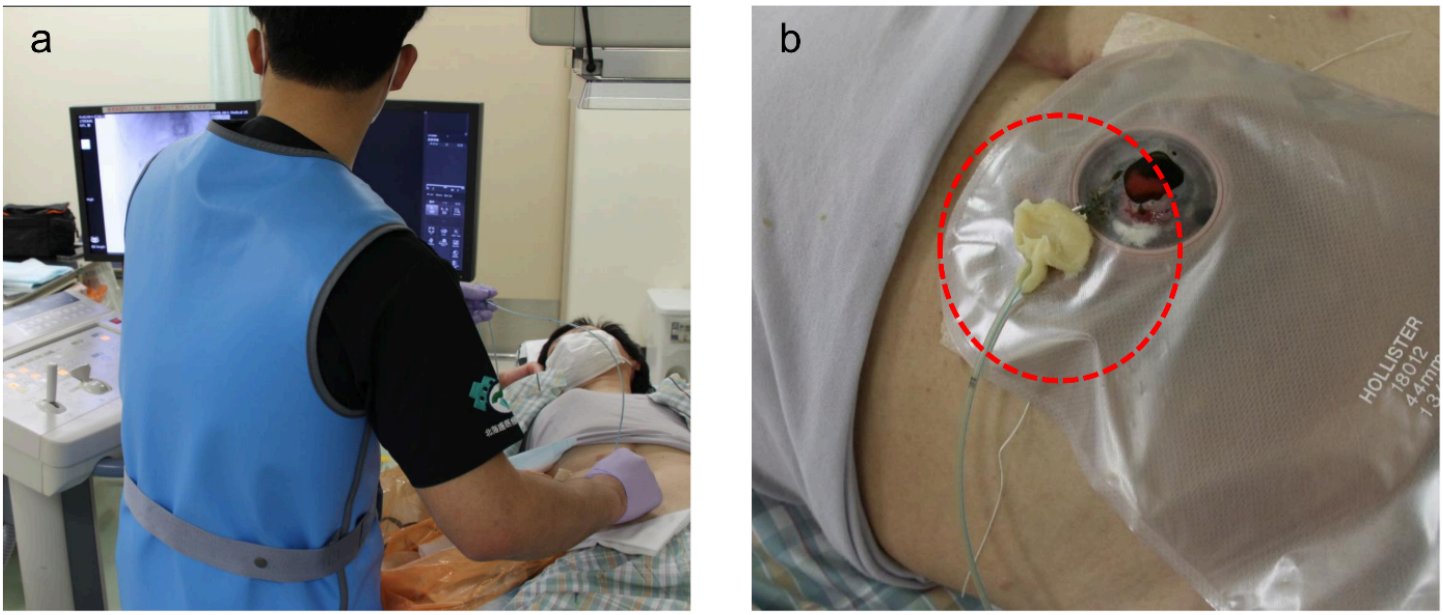

Figure 3

Technical aspects of tube placement and leakage prevention

(a) Anenteral tube was placed into the distal limb under fluoroscopic guidance. (b) To prevent leakage from the stoma appliance, the tube was passed through the ostomy pouch, and the puncture site was sealed withostomy barrier paste.