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ORIGINAL ARTICLE

Usefulness of colestimide for diarrhea in postoperative Crohn's disease

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Abstract

Background and Aim: Crohn's disease (CD) often causes intractable diarrhea after intestinal resection. Anion exchange resins have been reported to be effective in patients with bile acid diarrhea after distal ileectomy; furthermore, bile acid metabolism has been implicated in the pathogenesis of CD. Therefore, we aimed to examine the effectiveness of colestimide in the management of postoperative CD, and to compare its impact between patients with and those without ileocecal resection.

Methods: Postoperative CD patients prescribed colestimide for diarrhea between April 2017 and December 2020 were retrospectively evaluated for changes in the total Crohn's disease activity index (CDAI), each CDAI component including diarrhea frequency/week, albumin, and C-reactive protein (CRP) was evaluated before and after the administration of colestimide. Furthermore, comprehensive patient and physician assessments were reviewed from medical records during the first outpatient visit as a global clinical judgment after the initiation of colestimide therapy.

Results: A total of 24 patients were included, of whom 17 had a previous history of ileocecal resection. Significant improvement was noted in CDAI and diarrhea frequency only in the ileocecal resection group (CDAI: 114.5 $\pm$ 52.7 and 95.4 $\pm$ 34.8, $P < 0.05$; diarrhea frequency/week 23.8 $\pm$ 14.1 and 15.4 $\pm$ 11.2, $P < 0.05$, respectively). There was no significant improvement in other CDAI components, albumin level, or CRP level in either group. In the global clinical judgment, 13 and 4 patients in the ileocecal and non-ileocecal resection groups, respectively, were judged as "effective," with an overall efficacy rate of 70.8%.

Conclusion: Colestimide is effective for diarrhea in patients with postoperative CD, especially after ileocecal resection.

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Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease with repeated remission and relapse. Diarrhea is one of the major symptoms of CD.[1] It has been reported that approximately 50% of patients with CD require intestinal resection within 5 years and 60% within 10 years due to stenotic and/or perforating disease.[2] Recently, the surgery rate has decreased due to therapeutic advances[3]; however, many patients still require intestinal resection. One of the reasons for the lower quality of life in patients after intestinal resection is postoperative diarrhea, which is reported to occur in 24% of patients after subtotal colectomy and in 79% of patients after ileal resections >10 cm in length.[4] Diarrhea may be dependent or independent of inflammation.[5] One inflammation-independent diarrhea is bile acid diarrhea, which occurs because bile flows into the large intestine due to insufficient absorption of bile in the terminal ileum.[6] It has been reported that anion exchange resins, such as cholestyramine and colestimide, improve bile acid diarrhea by adsorbing bile acids in the gastrointestinal tract,[7] and colesevelam has been shown to be effective in the management of bile acid diarrhea in patients with CD.[8] However, it has been suggested that abnormal metabolism of secondary bile acids produced in the intestinal tract promotes an inflammatory response in the intestinal epithelium and exacerbates the pathogenesis of CD[9-14] and that resins inhibit intestinal inflammation.[9] Recently, a secondary bile acid, 3-oxolithocholic acid (3-oxoLCA), was reported to inhibit TH17 cells; moreover, TH17 cell activation due to decreased 3-oxoLCA may be involved in the pathogenesis of CD.[15] Therefore, this study aimed to examine the effectiveness of colestimide in the management of diarrhea in post-operative CD patients and to compare its impact between patients with and those without ileocecal resection.

Methods

Patients. We conducted a retrospective observational study using a prospective database of patients with inflammatory bowel disease at Kitasato University Kitasato Institute Hospital. Patients with CD with a history of bowel surgery who were prescribed colestimide between April 2017 and December 2020 were enrolled. The diagnosis of CD[16] was made clinically, endoscopically, and histologically based on national guidelines.

Clinical decisions regarding prescriptions were made by physicians during routine clinical practice. Colestimide was administered in the form of Corebine tablets 500 mg (Mitsubishi Tanabe Pharma Corporation, Osaka, Japan).

Evaluation. Clinical information was extracted from patients' medical records or the prospective patient database at Kitasato University Kitasato Institute Hospital, where Crohn's disease activity index (CDAI)[17] is routinely recorded for all patients with

CD at every visit. The primary endpoint was a change in diarrhea frequency, and the secondary endpoints were changes in CDAI, CDAI components other than diarrhea, C-reactive protein (CRP) level, and albumin level. The global clinical judgment was a comprehensive assessment of the effectiveness of the patient and specialist at the first outpatient visit after the initiation of colestimide therapy, retrospectively determined from the patient's medical record and classified as effective or ineffective. Adverse events were also assessed retrospectively from medical records. Patients were classified according to the presence or absence of a history of ileocecal resection (ileocecal resection group *vs* non-ileocecal resection group). Endoscopic findings were compared in patients who underwent endoscopy before and after the administration of colestimide without any changes in other treatments.

Statistical analysis. The Wilcoxon matched-pair signed-rank test was conducted to analyze the results before and after colestimide administration, and the chi-square test was used to compare the effective and ineffective groups according to the global clinical judgment of effectiveness. GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis. For all tests, a P-value <0.05 was considered statistically significant, and variables pertaining to accuracy were calculated with a 95% confidence interval (CI).

Ethical considerations. The study was conducted in accordance with the Declaration of Helsinki principles and Good Clinical Practice guidelines. The study protocol was approved by the Research Ethics Committee of Kitasato University Kitasato Institute Hospital (Kitasato University Kitasato Institute Hospital approval numbers: 13034, 21069). An opt-out process was used in this study, in which patients were provided with the opportunity to decline their participation based on the information available on the hospital's website.

Results

Patients. Twenty-four patients with CD with a history of bowel surgery were included in the study (Table 1). Of these, 17 patients had previously undergone ileocecal resection (ileocecal resection group). All seven patients in the non-ileocecal resection group had small bowel resections (ileum 3, jejunum 1, ileum, and jejunum 1, unknown details but did not receive ileocecal resection 2), while all five patients who underwent colorectal resection had a history of ileocecal resection. The number of surgeries in each patient ranged from 1 to 3 (median, 1), with 1 surgery in 15 (62.5%), 2 in 5 (20.8%), and 3 in 4 (16.7%) patients. One patient had a history of cholecystectomy at the commencement of treatment. The dose of colestimide was 1.5–3 g, which was taken three times a day in most patients (median 1.5 ± 0.81).

The average duration of treatment until the first visit was 55.5 ± 25.5 days. Colestimide was administered due to the lack of efficacy of single or combination anti-diarrheal agents in eight patients (47.1%), including six patients with loperamide hydrochloride, three patients with berberine chloride hydrate, two patients with albumin tannate, and one patient with ramocetron hydrochloride.

Overall effectiveness. A significant improvement was noted in CDAI (before: 138.8 ± 66.4, after: 115 ± 56.3, $P < 0.05$) (Table 2) after the administration of colestimide. Only the frequency of diarrhea per week (before: 26.1 ± 16.8, after: 19.7 ± 16.7, $P < 0.05$) showed a significant reduction among the

Table 1 Patient's characteristics

	Total ($n = 24$)
Sex, male, *n* (%)	15 (62.5)
Age (years), (mean ± SD)	44.5 ± 11.0
Disease duration (years), (mean ± SD)	20 ± 10.1
Montreal classification	
Age	
A1/A2/A3, *n* (%)	1 (4.35)/23 (95.8)/0 (0)
Location	
L1/L2/L3/L4, *n* (%)	13 (54.2)/0 (0)/11 (45.8)/0 (0)
Behavior	
B1/B2/B3/B4, *n* (%)	0 (0)/13 (54.2)/11 (45.8)/0 (0)
Elemental diet, *n* (%)	8 (33.3)
Anti-diarrheal drugs, *n* (%)	8 (33.3)
Anti-TNFα agents, *n* (%)	15 (62.5)
Thiopurines, *n* (%)	10 (41.7)
Number of operations	
1/2/3, *n* (%)	15 (62.5)/5 (20.8)/ 4 (16.7)
Surgical style	
With ileocecal resection	17 (70.8)
Only ileocecal resection, *n* (%)	3 (12.5)
Ileocecal + small bowel resection, *n* (%)	9 (37.5)
Ileocecal + small bowel + colorectal resection, *n* (%)	5 (20.8)
Non-ileocecal resection	
Only small bowel resection, *n* (%)	7 (29.2)
Only colorectal resection, *n* (%)	0 (0)
Length of remaining small bowel(cm), (mean ± SD)	307.4 ± 111.2 ($n = 15$)
Dose of colestimide (g)	
0.5/1/1.5/2/3, *n* (%)	1 (4.2)/1 (4.2)/ 12 (50.0)/1 (4.2)/9 (37.5)

Table 2 Changes in clinical parameters

	Total ($n = 24$)	
Oral administration of colestimide	Before	After
CDAI	138.8 ± 66.4	115 ± 56.3
	$P = 0.0178$*	
Frequency of diarrhea/week	26.1 ± 16.8	19.7 ± 16.7
	$P = 0.010$*	
Frequency of abdominal pain/week	1.79 ± 2.6	0.79 ± 2.23
	$P = 0.0703$	
Albumin (g/dL)	4.05 ± 0.58	4 ± 0.54
	$P = 0.4943$	
CRP (mg/dL)	0.22 ± 0.42	0.44 ± 0.99
	$P = 0.2306$	

CDAI, Crohn's disease activity index; CRP, C-reactive protein.

Table 3 Comparison between patients with ileocecal resection or non-ileocecal resection

	Ileocecal resection group ($n = 17$)		Non-ileocecal resection group ($n = 7$)	
Oral administration of colestimide	Before	After	Before	After
CDAI	114.5 ± 52.7	95.4 ± 34.8	197.9 ± 47.9	165.6 ± 52.8
	$P = 0.0347$*		$P = 0.2969$	
Frequency of diarrhea/week	23.8 ± 14.1	15.4 ± 11.2	31.7 ± 24.5	30 ± 24.7
	$P = 0.0002$*		$P = 0.9375$	
Frequency of abdominal pain/week	1.06 ± 1.69	0.56 ± 1.26	3.25 ± 3.54	1.25 ± 3.54
	$P = 0.2500$		$P = 0.1875$	
Albumin (g/dL)	4.10 ± 0.64	4.07 ± 0.58	3.93 ± 0.46	3.83 ± 0.42
	$P = 0.6763$		$P = 0.7500$	
CRP (mg/dL)	0.14 ± 0.27	0.19 ± 0.29	0.42 ± 0.71	1.06 ± 1.86
	$P = 0.1304$		$P = 0.7188$	

CDAI, Crohn's disease activity index; CRP, C-reactive protein.

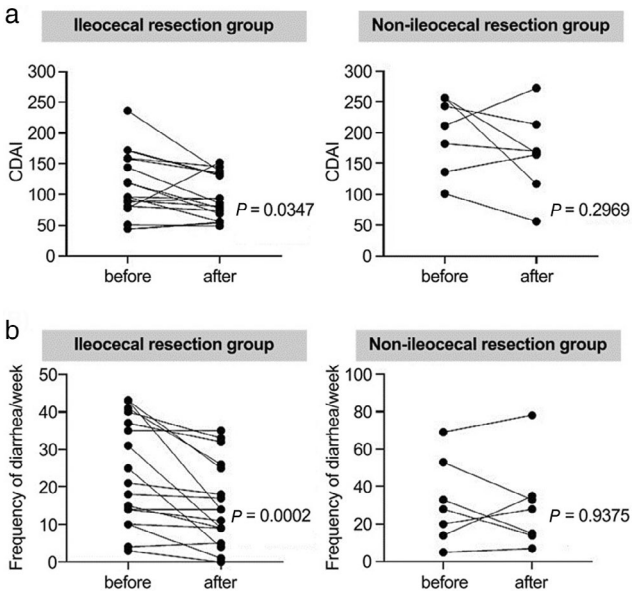

Figure 1 Change in Crohn's disease activity index (CDAI) (a) and diarrhea frequency (b) after the initiation of colestimide in the ileocecal resection or non-ileocecal resection groups. Wilcoxon signed-rank test.

components of CDAI, while all other components (frequency of abdominal pain, and general well-being) remained unchanged. There was no significant improvement in both CRP and albumin (CRP: 0.22 ± 0.42 and 0.44 ± 0.99, $P = 0.2306$; albumin: 4.05 ± 0.58 and 4 ± 0.54, $P = 0.4943$, before and after prescription, respectively) (Table 2).

Of the six patients who were on loperamide hydrochloride, two patients were able to discontinue it after initiating colestimide because of improvement in diarrhea.

Comparison by surgical procedure. When assessing effectiveness based on the history of ileocecal resection, significant improvement was observed in CDAI and diarrhea frequency only in the ileocecal resection group (CDAI: 114.5 ± 52.7 and 95.4 ± 34.8, $P < 0.05$; frequency of diarrhea/week 23.8 ± 14.1 and 15.4 ± 11.2, $P < 0.05$, before and after prescription, respectively) (Table 3, Fig. 1). There was no significant improvement in the other CDAI components and albumin levels. CRP was also not improved either in the ileocecal resection group (before: 0.14 ± 0.27, after: 0.19 ± 0.29, $P = 0.1304$) or in the non-ileocecal resection group (before: 0.42 ± 0.71, after: 1.06 ± 1.86, $P = 0.7188$).

Comparison by global clinical judgment. In a comprehensive evaluation of global clinical judgment, 13 of 17 patients in the ileocecal resection group and four of seven patients in the non-ileocecal resection group were rated as "effective" (the overall efficacy rate was 70.8% [17/24]). None of the baseline factors were significantly associated with effectiveness in all patients (Table 4). In addition, we explored baseline factors predicting effectiveness in the ileocecal resection group separately but found no significant factors (Table 5). Concomitant use of anti-diarrheal agents at baseline did not affect effectiveness (effective, $n = 6$; ineffective, $n = 2$).

Endoscopic findings. We compared endoscopic findings in patients whose endoscopy before and after the administration of colestimide without any changes in other treatment was available ($n = 13$, mean duration before and after colestimide, 12.2 and 18.8 months, respectively). Only one patient had an active endoscopic lesion at baseline (a simple endoscopic score for Crohn's disease [SES-CD] of 9). One patient had a worsening of SES-CD from 0 to 3 points, while all other patients ($n = 12$) including a patient with a baseline SES-CD of 9 had no change in SES-CD.

Adverse events. Three patients developed constipation, of whom two patients discontinued treatment, while one continued with dose reduction (from 3 to 2 g per day), and one patient had epigastric pain, which resolved after the cessation of colestimide. The dosage was 3 and 1.5 g per day in two cases of constipation and 1.5 g per day in one case of epigastric pain.

Discussion

This real-world retrospective study examined the clinical usefulness of colestimide in improving diarrhea in postoperative CD patients and found that improvement in diarrhea frequency was

Table 4 Factors associated with clinical effectiveness based on global clinical judgment

	Effective group ($n = 17$)	Ineffective group ($n = 7$)	*P*-value	OR (95% CI)
Sex, male (*vs* female), *n* (%)	10 (58.9)	5 (71.4)	0.5621	0.6 (0.1–3.2)
Montreal classification				
Location				
L1 (*vs* L3), *n* (%)	11 (64.7)	2 (28.6)	0.1063	4.6 (0.8–26.7)
Behavior				
B2 (*vs* B3), *n* (%)	10 (58.9)	3 (42.9)	0.4755	1.9 (0.4–9.2)
Number of operations, (mean ± SD)	1.53 ± 0.80	1.57 ± 0.79		
Once (*vs* ≥2 times), *n* (%)	11 (64.7)	4 (57.1)	0.7279	1.4 (0.3–9.2)
Surgical style				
With ileocecal resection, *n* (%)	13 (76.4)	4 (57.1)	0.3437	2.4 (0.4–17.0)
Amount of colestimide (g) (mean ± SD)	2.06 ± 0.86	1.93 ± 0.73		
3 g (*vs* <3 g), *n* (%)	7 (41.2)	2 (28.6)	0.5621	1.8 (0.3–10.5)
Elemental diet, *n* (%)	6 (35.3)	2 (28.6)	0.7508	1.4 (0.2–8.3)
Anti-diarrheal drugs, *n* (%)	5 (29.4)	3 (42.9)	0.5907	0.6 (0.1–2.9)
Anti-TNFα agents, *n* (%)	9 (53.3)	5 (71.4)	0.4037	0.5 (0.1–2.5)
Thiopurines, *n* (%)	9 (53.3)	3 (42.9)	0.6534	1.5 (0.3–7.3)
Frequency of diarrhea/week (mean ± SD)	26.8 ± 15	24.3 ± 9.8		
>20 (*vs* ≤20), *n* (%)	11 (64.7)	2 (28.6)	0.1063	4.6 (0.8–26.7)
CRP (mg/dL) (mean ± SD)	0.14 ± 0.27	0.40 ± 0.66		
<0.1 (*vs* ≥0.1)	11 (64.7)	3 (42.9)	0.3237	2.4 (0.5–12.0)

CI, confidence interval; CRP, C-reactive protein.

Table 5 Factors associated with clinical effectiveness based on global clinical judgment in the ileocecal resection group

	Ileocecal resection effective group ($n = 13$)	Ileocecal resection ineffective group ($n = 4$)	*P*-value	OR (95% CI)
Sex, male (*vs* female), *n* (%)	8 (61.5)	3 (75.0)	0.6223	0.5 (0.03–4.7)
Montreal classification				
Location				
L1 (*vs* L3), *n* (%)	7 (53.8)	1 (25.0)	0.3121	3.5 (0.4–51.0)
Behavior				
B2 (*vs* B3), *n* (%)	8 (61.5)	2 (50.0)	0.6816	1.6 (0.2–12.3)
Number of operations				
Once (*vs* ≥2 times), *n* (%)	8 (61.5)	2 (50.0)	0.6816	1.6 (0.2–12.3)
Surgical style				
With colorectal resection, *n* (%)	4 (30.8)	1 (25.0)	0.8247	1.3 (0.1–21.2)
Amount of colestimide (g)				
3 g (*vs* <3 g), *n* (%)	4 (30.8)	1 (25)	0.8247	1.3 (0.1–21.2)
Elemental diet, *n* (%)	5 (38.5)	0 (0)	0.1399	
Anti-diarrheal drug, *n* (%)	3 (23.1)	1 (25.0)	0.9368	0.9 (0.1–15.2)
Anti-TNFα agents, *n* (%)	8 (61.5)	2 (50)	0.6818	1.6 (0.2–12.4)
Thiopurines, *n* (%)	7 (53.8)	1 (25.0)	0.3121	3.5 (0.4–51.0)
Frequency of diarrhea/week (mean ± SD)				
>20 (*vs* ≤20), *n* (%)	8 (61.5)	1 (25)	0.2004	4.8 (0.5–68.8)
CRP (mg/dL) (mean ± SD)				
<0.1 (*vs* ≥0.1)	9 (69.2)	2 (50.0)	0.4816	2.3 (0.3–17.6)

CI, confidence interval; CRP, C-reactive protein.

significant only in the ileocecal resection group and that there was no improvement in parameters other than diarrhea frequency.

There are a variety of different types of postoperative diarrhea, including (i) interruption of the ileal brake, which reduces gastric emptying, prolongs small intestinal transit time, and reduces both gastric and pancreatic secretion[18]; (ii) bacterial overgrowth in the small bowel[19]; (iii) diarrhea due to inflammation of CD; (iv) bile acid diarrhea caused by the malabsorption of bile acid in the ileum; and (v) irritable bowel syndrome overlapping with the postoperative condition. The treatment of these conditions includes surgical procedures, dietary therapy, and pharmacotherapy, such as digestive enzymes, vitamins,

antibiotics, anion exchange resins, opium tincture, codeine, and antidiarrheals. Oral loperamide is one of the most widely used antidiarrheal drugs in postoperative patients, which acts by reducing intestinal peristalsis and promoting intestinal water absorption. In this study, two of six patients who were on loperamide not only responded to colestimide but were also able to discontinue loperamide. This suggests that colestimide may be effective in the management of diarrhea that is unresponsive to loperamide.

Bile acid diarrhea is classified into three types: type 1 is secondary to ileal dysfunction, such as CD itself or post-ileocecal resection; type 2 is idiopathic, such as primary bile acid diarrhea or irritable bowel syndrome; and type 3 is secondary to gastrointestinal disorders that are unrelated to ileal dysfunction, such as after cholecystectomy and CD.[20] The effectiveness of colestimide has been reported for all three types.[21]

Bile acid diarrhea occurs in 11–14% of patients with CD without a history of intestinal resection.[22] Since a reduction in the expression of sodium-dependent bile transporters in the intestine is reported to cause bile acid diarrhea in CD,[23] it may be efficacious in patients without terminal ileal resection. However, in our study, the reduction in diarrhea frequency was significant only in the ileocecal resection group, and the effectiveness of bile acid diarrhea following ileocecal resection seemed to be greater than that caused by CD pathogenesis.

In contrast, some studies have reported that bile acid metabolism is involved in the pathophysiology of CD.[9-14] The concentration of bile acids in the bile of CD patients is elevated compared with that in healthy individuals, and the production of 7α-hydroxy-4-cholesterin-3-one (C4), a precursor of bile acids, is increased due to the malabsorption of bile acids.[25] In addition, fibroblast growth factor 19 (FGF19), which regulates bile acid synthesis, is decreased in patients with CD.[24] Patients with ileal dysfunction, including those with post-ileocecal resection or those with active disease in the ileum, are reported to have higher bile acid concentration, higher C4, and lower FGF19 in bile.[24,25] These reports suggest that bile malabsorption may also occur in patients with CD with the active ileal disease without ileocecal resection. Most of the patients included in this study had relatively mild inflammation, and further studies are needed to examine the efficacy of colestimide in patients with moderate-to-severe disease.

To the best of our knowledge, no studies have reported the use of bile acid resins after bowel surgeries other than ileocecal resection. In our study, although there was no change in the frequency of diarrhea in the non-ileocecal resection group, the presence of a previous history of ileocecal resection was not a significant factor for effectiveness in the analysis of the global clinical judgment. These results suggest that the presence of a prior history of ileocecal resection may not be the sole factor and each patient has a different degree of postoperative bile acid malabsorption. It may be interesting to see if an objective assessment of bile acid malabsorption by 75Se-labeled homocholic acid-taurine (75SeHCAT) could predict the efficacy of colestimide.[26]

This study has several limitations. First, due to the retrospective nature of the study, we were unable to obtain sufficient information, such as detailed surgical procedures and the length of the remaining small bowel. However, there was no difference in the effectiveness of colestimide according to the number of previous surgeries. Second, the degree of inflammation before and after administration was not evaluated using objective measures, such as endoscopy. However, in our study, the CDAI was prospectively recorded in our routine practice, which could have minimized the potential bias. Third, because of the small sample size, the statistical power to detect the effectiveness of colestimide was low and multivariate analysis was not possible. Lastly, the anti-inflammatory effect could not be sufficiently examined because most patients had low inflammatory disease activity due to the postsurgical clinical settings. Therefore, larger and well-designed clinical studies are warranted.

In conclusion, colestimide is effective in the management of diarrhea in patients with postoperative CD, especially after ileocecal resection.

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