A Simple 1-Day Colon Capsule Endoscopy Procedure Demonstrated to be a Highly Acceptable Monitoring Tool for Ulcerative Colitis

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Background: Second-generation colon capsule endoscopy (CCE-2) has been reported as a potential tool for monitoring ulcerative colitis (UC). However, its excretion rate is still unsatisfactory, and the bowel preparation regimen is not well tolerated. Furthermore, a standard bowel preparation regimen validated for UC has not been established. The aim of this study was to develop a simple 1-day CCE-2 procedure while evaluating its excretion rate and acceptability in UC. Factors associated with the colonic transit time and acceptability of CCE-2 were evaluated.

Methods: Thirty-three patients were prospectively evaluated. Five hundred milliliters of hypertonic polyethylene glycol solution, followed by 250 mL of water, was ingested 2.5 hours before, then 1, 3, and 6 hours after capsule ingestion until its excretion, with castor oil added to the second ingestion. Mayo endoscopic subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) were graded, and their correlations with fecal calprotectin (FC) were assessed. A questionnaire comparing CCE-2 with previous colonoscopy (CS) was conducted.

Results: The excretion rate was 93.9% (31/33). The acceptability of CCE-2 was superior to CS (CCE-2 42.4% vs CS 27.3%). The median colonic transit time was 119 minutes and showed a positive correlation with MES ($P = 0.010$), UCEIS ($P = 0.010$), and FC ($P = 0.041$). CCE-2 was not favored by patients whose colonic transit times were longer.

Conclusions: A novel bowel preparation regimen of CCE-2 was well tolerated, with a high excretion rate, by UC patients. Patients with active disease required longer colonic transit time, which may have resulted in the lower acceptability of CCE-2.

Key Words: ulcerative colitis, colon capsule endoscopy, bowel preparation regimen

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colonic mucosa characterized by a relapsing-remitting course. In recent years, mucosal healing (MH), the resolution of visible mucosal inflammation and ulceration, has been shown to be associated with a lower risk of disease relapse, hospitalization, colectomy, and colitis-associated cancer compared with moderate to severe mucosal inflammation in patients with UC.[1–7] Thus, the target of therapy in UC has become to achieve MH. In clinical practice, frequent colonoscopy (CS) is required for monitoring mucosal status during the therapeutic management of UC as MH is difficult to predict from clinical symptoms.[8] However, frequent CS could be a burden on patients, and there is a concern that CS may cause disease flare by direct trauma to the mucosa or by air insufflation.[9]

Second-generation colon capsule endoscopy (CCE-2) has been drawing attention as a noninvasive tool for UC[10–16] and has a strong correlation in determining disease activity, defined by Mayo endoscopic subscore (MES) and Matts endoscopic score with CS[11, 14, 15]; however, there are some issues with the practical use of CCE-2 in UC. First, the excretion rate of CCE-2 is still unsatisfactory as a monitoring tool in UC as failure to observe the entire colon leads to areas with disease involvement being missed. Second, acceptability of CCE-2 is insufficient, especially due to the larger volume of bowel preparation compared with CS. Furthermore, a standard bowel preparation regimen validated for UC has not been established.

The aim of this study was to develop a simple 1-day CCE-2 procedure optimized for UC and evaluate its excretion rate and acceptability as a monitoring tool. The whole

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procedure was designed to be completed within a day or less with reduced volume bowel preparation, which does not require any diet restrictions or laxatives on the day before the procedure. The factors associated with the excretion rate, more specifically the colonic transit time and patient acceptability of CCE-2, were also assessed.

METHODS

Patients

From August 2016 to May 2017, patients aged 20 to 80 years who had been diagnosed with UC and who were scheduled to undergo CCE-2 were recruited for the study. Exclusion criteria included presence of dysphagia, higher risk of capsule retention (eg, history of radiation enteropathy, intestinal surgery, or intestinal obstruction), renal insufficiency, pacemaker or other implanted electromedical devices, current pregnancy, or with a contraindication to hypertonic polyethylene glycol solution (PEG), castor oil, metoclopramide, or dimethicone.

Bowel Preparation Regimen

The bowel preparation regimen used in this study is shown in Table 1. No dietary restrictions or laxatives were taken on the day before the procedure. On the day of the procedure, patients were instructed to take 500 mL of PEG (MOVIPREP; EA Pharma, Tokyo, Japan) and 250 mL of water at 6:30 am at home. The capsule (PillCam COLON 2 Capsule; Medtronic, Minneapolis, MN, USA) was ingested at 9:00 am when they arrived at the hospital. Once the capsule was confirmed to be in the small intestine, patients were allowed to leave the hospital after taking a first booster consisting of 500 mL of PEG and 250 mL of water, with 20 mL of castor oil as an enterokinetic agent in all cases. If the capsule was retained in the stomach an hour after its ingestion, a 10-mg metoclopramide tablet was given. Additional boosters were taken at 12:00 pm and at 3:00 pm until the capsule was excreted. The patients were allowed to resume their diet at 4:00 pm, and CCE-2 recording continued until the battery ran out (battery capacity of approximately 10 hours) or the capsule was excreted. Patients were followed up the day after the procedure to evaluate changes in their well-being and to confirm if the capsule had been excreted. When capsule retention was suspected, an abdominal radiograph was obtained to examine the location of the capsule. Questionnaires comparing CCE-2 with previous CS were answered by all of the enrolled patients.

Reading of Capsule Videos

All CCE-2 videos in this study were assessed blindly by 2 endoscopists experienced in clinical management of UC and small bowel capsule endoscopy. The MES and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) were used to grade mucosal inflammation, and a 4-point scale was used to grade the colon cleansing levels as excellent, good, fair, or poor for each segment of the colon, as previously described[17]; image samples of each colon-cleansing level are shown in Figure 1. Cleansing levels of fair, good, and excellent were considered acceptable in this study, based on a previous report.[16] The capsule excretion rate and transit times in each segment of the gastrointestinal tract (stomach, small intestine, colon [cecum and ascending colon, transverse colon, descending and sigmoid colon], and rectum) were evaluated.

Stool Samples for Fecal Calprotectin Assays

Stool samples from the 3 days prior to the CCE-2 were collected from patients on the day of the procedure and were stored at –20°C until measurement of fecal calprotectin (FC). FC was assayed based on colloidal gold aggregation using an NS-Prime automatic analyzer (Alfresa Pharma Co., Ltd, Osaka, Japan).

TABLE 1: Bowel Preparation Regimen

Day	Hour	Procedure
Day before examination		No dietary restrictions or laxatives
Examination day	AM 6:30	500 mL PEG and 250 mL water
	AM 9:00	Ingest CCE-2 with dimethicone at the hospital
	AM 10:00	500 mL PEG and 250 mL water with 20 mL castor oil once CCE-2 is confirmed in the small intestine
		(Add metoclopramide 10 mg tablet if CCE-2 remains in the stomach)
		Patients are allowed to leave the hospital
	PM 12:00	500 mL PEG and 250 mL water if CCE-2 has not been excreted
	PM 3:00	500 mL PEG and 250 mL water if CCE-2 has not been excreted
	PM 4:00	Patients are allowed to resume their diet
		CCE-2 recording continues until the battery runs out or is excreted

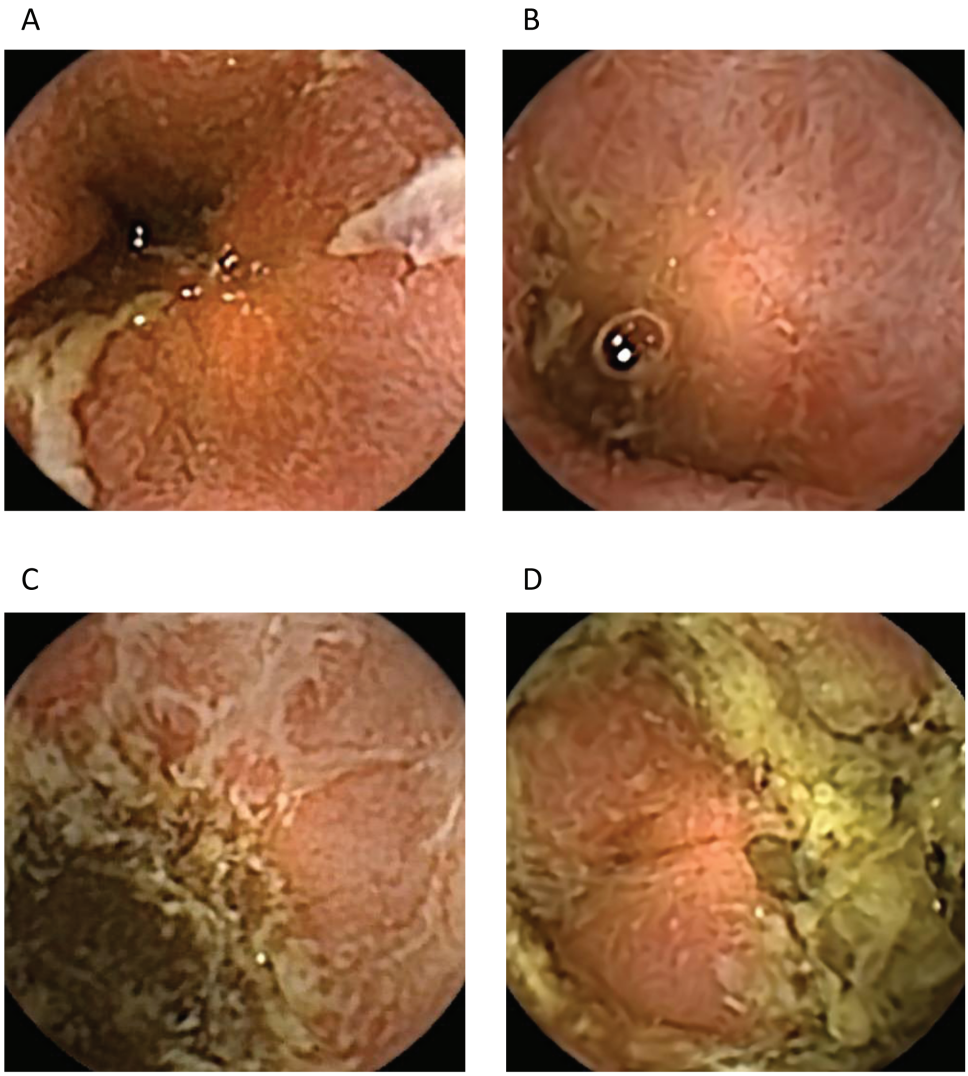

FIGURE 1. Representative images of colon cleansing rated on a 4-point scale. A, Excellent. B, Good. C, Fair. D, Poor.

Questionnaire for Colon Capsule Endoscopy

A questionnaire was administered to all patients in this study to determine the acceptability of CCE-2. The questionnaire consisted of the following 4 questions: (1) In your next endoscopic examination, which would you choose CCE-2 or CS?; (2) How satisfied were you with the bowel preparation regimen of CCE-2 compared with previous CS?; (3) What did you feel were the advantages of CCE-2 compared with previous CS?; (4) What did you feel were the drawbacks for CCE-2 compared with previous CS?

Statistical Analysis

All numerical values are shown as the median with the range in parentheses or average ± SEM. The differences between the 2 groups were analyzed using the Mann-Whitney *U* test, Fisher exact test, and chi-square test in univariate analyses, and a logistic regression model in multivariate analysis. A Spearman rank correlation coefficient was used to analyze the correlation between MES and FC, and UCEIS and FC. Receiver operator characteristic (ROC) curve analysis was used to determine the predictive value of FC for MES (MES0 vs MES1-3). Interobserver agreements for MES, each item, and total UCEIS score were analyzed using kappa (κ) values in every patient who completed the procedure. A κ value <0.4 was considered fair to poor; between 0.4 and 0.6 was considered moderate; between 0.6 and 0.8 was considered substantial; and ≥0.8 suggested perfect agreement.[18] A *P* value of ≤0.05 was considered statistically significant, and variables pertaining to accuracy were calculated with 95% confidence intervals. Statistical analyses were performed using SPSS software, version 20.0, and Prism software, version 6.0.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The Research Ethics Committee of Kitasato University Kitasato Institute Hospital approved the study protocol and all documents (approval number: 16028). Written informed consent was obtained from all patients included in this study.

RESULTS

Study Population

A total of 39 consecutive patients were prospectively enrolled. Four patients were excluded because they mixed up our split-dose bowel preparation with the standard single-dose regimen for CS and took the entire dose (2 L) in the morning. Thus, 35 patients were included in the analysis. Among the 35 patients, 2 patients were excluded because of their inability to ingest the booster doses after administering castor oil. Thus, 33 patients who completed the bowel preparation regimen were evaluated in the accurate analysis, and their demographic characteristics are shown in Table 2.

Capsule Excretion Rate and Transit Time

The capsule excretion rate within the battery life was 93.9% (31/33); in 1 patient, the capsule was retained in the cecum and excreted 2 days after ingestion. The other patient had delayed excretion due to a slow transit in the inflamed areas of the colon and excreted the capsule 30 minutes after the battery died.

The 31 patients who excreted the capsule within the battery life were evaluated for the examination time and transit time in each segment of the gastrointestinal tract. The median examination time (range) was 227 (81–733) minutes, and the median colonic transit time was 119 (8–489) minutes regardless of the use of metoclopramide (n = 2).

TABLE 2: Baseline Characteristics of Included Patients

Characteristics	n = 33
Age, median (range), y	40 (22–70)
Male, No. (%)	16 (48.5)
Disease duration, median (range), y	11.3 (0–27)
Extent of disease, No. (%)	
Total	18 (54.6)
Left-sided	14 (42.4)
Proctitis	1 (3.0)
Clinical disease activity, No. (%)	
Partial Mayo score ≤ 2	25 (75.8)
Partial Mayo score > 2	8 (24.2)
Fecal calprotectin, median (range), μg/g	241 (8–12,364)
Medications, No. (%)	
5-ASA/SASP	32 (97.0)
6-MP/AZA	12 (36.4)
Anti-TNFα	6 (18.2)
PSL	2 (6.1)
Tac	1 (3.0)
No medication	1 (3.0)

Abbreviations: 5-ASA, 5–aminosalicylic acid; 6-MP, 6-mercaptopurine; anti-TNFα, anti–tumor necrosis factor–alpha therapy (infliximab or adalimumab); AZA, azathioprine; PSL, prednisolone; SASP, salazosulfapyridine; Tac, tacrolimus.

Bowel Preparation

The required PEG volumes and colon cleansing levels were assessed. The average volume of PEG required to complete the procedure was 1.45 ± 0.07 L. Eleven patients (35.5%) excreted the capsules after taking ≤1 L PEG, and 11 patients (35.5%) required 1–1.5 L PEG. Only 2 patients (6.1%) required metoclopramide. The rates of overall colon cleansing levels among 127 segments assessed as excellent/good/fair/poor were 12.6%/31.5%/33.1%/22.8%, respectively; the rate of the acceptable level (excellent to fair) was 77.2%. Among 85 segments in 22 patients with MES 0–1, the acceptable level was achieved in 88.2%, which was significantly higher than that in 11 patients with MES 2–3 (54.8%, n = 42 segments; $P < 0.0001$).

Correlation Between FC and Either MES or UCEIS

FC was compared with the endoscopic findings of CCE-2. FC showed significantly positive correlations with MES (Fig. 2A) and UCEIS (Fig. 2B), with r values of 0.7456 and 0.7235, respectively. As a result of ROC analysis, FC predicted an MES of 0 with a high area under the curve value of 0.9786 (Fig. 2C). When the cutoff level of FC was set to 64 μg/g, FC below 64 μg/g predicted an MES of 0 with a sensitivity of 100%, specificity of 84.6%, positive predictive value of 90.0%, and negative predictive value of 100%.

Interobserver Agreement of Endoscopic Findings of CCE-2

Interobserver agreement of MES was substantial (κ = 0.746) (Table 3). As for UCEIS, the overall agreement between the interobservers was substantial (κ = 0.684); assessing vascular pattern and bleeding had perfect agreement, with κ values of 0.859 and 1.000, respectively, whereas erosions and ulcers had substantial agreement, with a κ value of 0.610. Although ulcers or multiple erosions were easily detected, it was difficult to detect erosions if the patients had only a small number of them.

Factors Associated With Colonic Transit Time

Factors associated with colonic transit time were evaluated in univariate analyses. Age, sex, and partial Mayo score showed no association, while significant associations were noted with the MES, UCEIS, and FC, with P values of 0.010,

0.010, and 0.041, respectively (Fig. 3). The presence of colonic mucosal inflammation, as determined by higher MES, UCEIS, and FC, correlated with longer colonic transit times.

Results of Questionnaires Concerning CCE-2 Compared With Previous CS

Questionnaires showed that 42.4% (14/33) and 27.3% (9/33) of patients preferred CCE-2 and CS, respectively, and 30.3% (10/33) did not have a preference. The most favorable aspect of CCE-2, according to the majority of the patients (75.8%), was its noninvasive feature, followed by the procedure being completed outside the hospital (30.3%). However, about half of the patients (42.4%) were dissatisfied with the devices, and some patients (33.3%) were dissatisfied with the bowel preparation regimen, especially the taste and volume of PEG. Focusing on our bowel preparation regimen, 72.7% (24/33) had no aversion to and 27.3% (9/33) preferred our bowel preparation regimen, compared with the standard bowel preparation regimen for CS, which requires 1–2 L PEG to be taken all at once over a short period.

Factors Associated With the Acceptability of CCE-2

Clinical disease activity and colonic transit time were significantly associated with the acceptability of CCE-2 in univariate analyses, with *P* values of 0.046 and 0.026, respectively (Table 4). However, in a multivariate logistic regression model, colonic transit time was independently associated with acceptability (odds ratio, 1.01; 95% confidence interval, 1.00–1.02; $P = 0.042$), whereas clinical disease activity was not.

Adverse Events

No serious adverse event was reported in this study. A total of 2 (5.1%) adverse events, namely nausea and discomfort, were reported from the enrolled 39 patients; both were attributed to the castor oil and PEG, which were resolved within the same day of the procedure. Three patients (7.7%) were required to take an abdominal radiograph to exclude capsule retention because the capsules were not excreted within 24 hours, but they were eventually excreted in all cases.

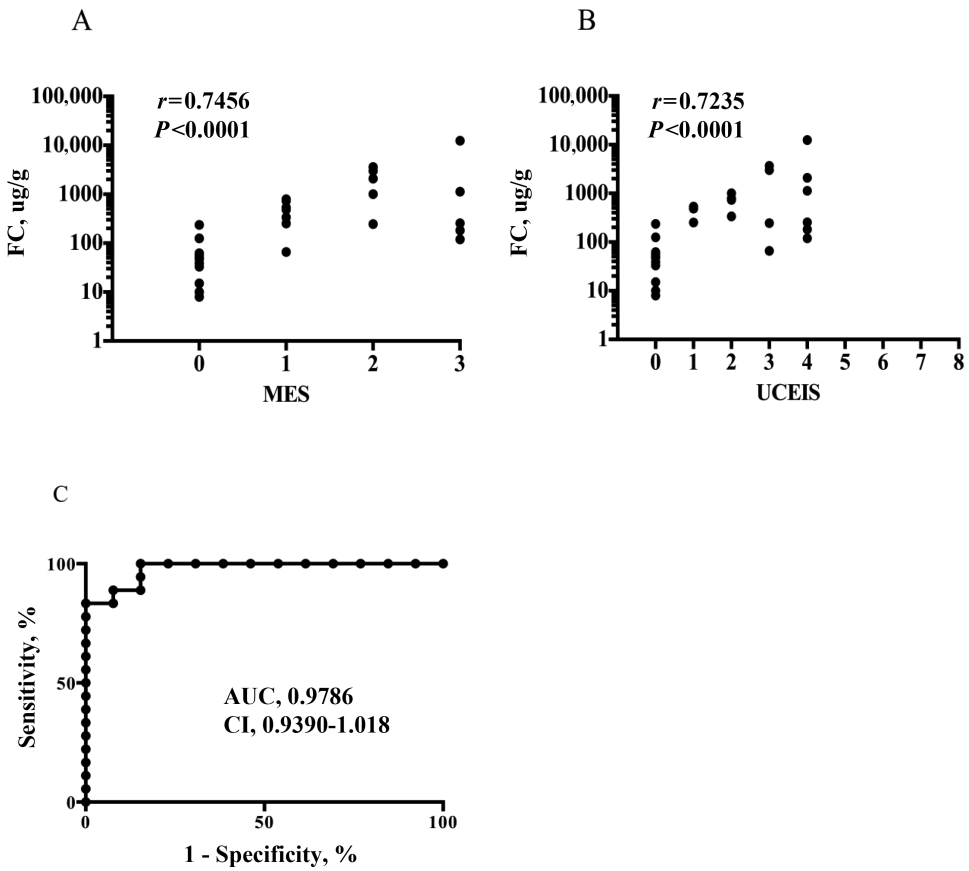

FIGURE 2. Spearman correlation between fecal calprotectin and either (A) MES or (B) UCEIS. A base-10 log scale is used for the *y* axis. C, The receiver operating characteristic curve determined the predictive value of FC for MES (MES 0 vs MES 1–3).

DISCUSSION

We described a novel bowel preparation regimen for CCE-2 in UC with a high excretion rate and acceptability, and to our knowledge, this is the first report to evaluate the factors associated with these 2 aspects, which will help to optimize the use of CCE-2 in clinical practice for UC.

CCE-2 is a tool that can be used to physiologically observe the entire colon, and its most advantageous feature is its noninvasiveness; this may not be solely due to its painlessness, but also the fact that it does not require air insufflation, which eliminates the risk of colonic bloating. Further, the psychological and physical stress of the procedure is minimal.[19–21] For UC patients who require frequent endoscopy during the course of their disease, these features may be helpful for monitoring disease activity and avoiding disease exacerbation by CS.[9]

Despite the advantages mentioned above, there are some concerns that prevent CCE-2 from being widely used for UC, namely the risk of incomplete observation and a large volume of bowel preparation. Therefore, achieving a high excretion rate and reducing the volume of bowel preparation are essential,

TABLE 3: Interobserver Variability of Endoscopic Findings (κ value; n = 31)

		UCEIS		
MES [0–3]	Vascular [0–2]	Bleeding [0–3]	Erosions and Ulcers [0–3]	Total Score [0–8]
0.746	0.859	1.000	0.610	0.684

As shown, interobserver agreement of MES and total score of UCEIS were substantial. Although ulcers or multiple erosions were easily detected, it was difficult to detect erosions if the patients had only a small number of them.

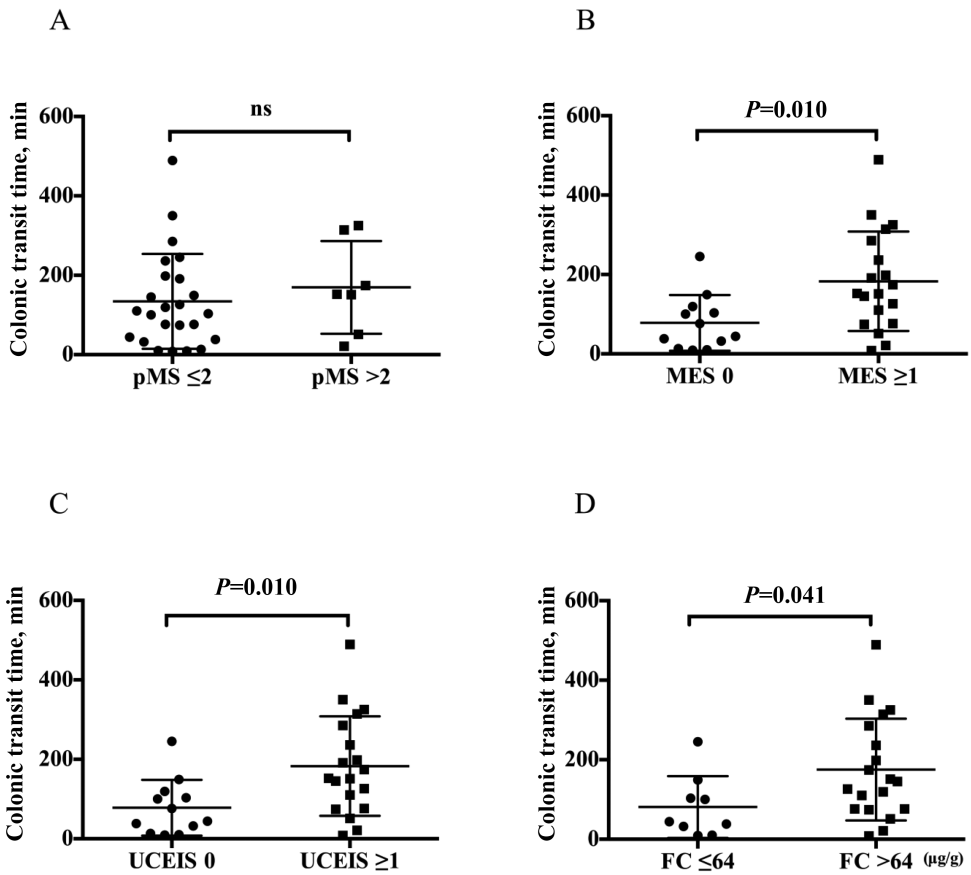

FIGURE 3. Univariate analyses on the colonic transit time in disease activity. Significant associations were noted with the MES, UCEIS, and FC, determined by Mann-Whitney *U* test. A, Partial Mayo score (pMS ≤ 2, pMS > 2; *P* = 0.313). B, MES (MES = 0, MES ≥ 1). C, UCEIS (UCEIS = 0, UCEIS ≥ 1). D, FC (FC ≤ 64, FC > 64).

TABLE 4: Factors Associated With the Acceptability of CCE-2; the Number of Patients Who Preferred CCE-2 or CS/Had No Preference in the Questionnaire

	CCE-2	CS or No Preference	*P*
Age, No. (%)			
≤40 y	8 (24.2)	11 (33.3)	0.733
>40 y	7 (21.2)	7 (21.2)	
Sex, No. (%)			
Male	9 (27.3)	7 (21.2)	0.303
Female	6 (18.2)	11 (33.3)	
Disease duration, mean ± SEM, y	11.3 ± 2.2	14.6 ± 2.2	0.297
Clinical disease activity, No. (%)			
Partial Mayo score ≤ 2	14 (42.4)	11 (33.3)	0.046
Partial Mayo score > 2	1 (3.0)	7 (21.2)	
Extent of disease, No. (%)			
Total	8 (24.4)	10 (30.3)	0.620
Left-sided	7 (21.2)	7 (21.2)	
Proctitis	0 (0)	1 (3.0)	
Mayo endoscopic subscore, No. (%)			
MES 0	8 (24.2)	4 (12.1)	0.187
MES 1	4 (12.1)	5 (15.2)	
MES 2	1 (3.0)	4 (12.1)	
MES 3	1 (3.0)	4 (12.1)	
Colonic transit time, mean ± SEM, min	91.2 ± 24.4	184.5 ± 29.8	0.026
Fecal calprotectin, mean ± SEM, μg/g	467.3 ± 292.7	722.6 ± 237.3	0.500

Of note, clinical disease activity and colonic transit time were significantly associated with the acceptability of CCE-2 in univariate analyses; however, in multivariate analyses, colonic transit time was independently associated, while clinical disease activity was not.

however, there is insufficient evidence for the appropriate use of CCE-2, especially regarding the bowel preparation regimen, in UC.[10–16]

In general, it is important to maintain an appropriate balance between the excretion rate, acceptability and cleansing levels when performing CCE-2 for polyp surveillance.[22] However, it is suggested that a high cleansing level is not always necessary for monitoring UC activity, unlike polyp surveillance,[11, 16] and that a cleansing level of "fair" could be enough to accurately evaluate the mucosal status because endoscopic characteristics of mucosal inflammation in UC are continuous and diffuse. Therefore, excretion rate and acceptability are more essential in UC: a high excretion rate in order not to miss lesions, especially in the distal colorectum, and acceptability to tolerate frequent endoscopy. Focusing on these 2 points, we performed a prospective study to evaluate our simple bowel preparation regimen optimized for UC. Previous publications used 3–6 L of bowel preparation including multiple booster doses and prokinetics as a standard bowel preparation regimen for CCE-2,[10–15, 23–26] and the preparation has to be started a few days prior to the procedure with dietary restrictions or laxative use. We hypothesized that capsule excretion was dependent mostly on the booster doses and that cutting down considerably on the volume of PEG for bowel cleansing would be feasible, as a high cleansing level is not required for determining disease activity in UC.[11, 16, 23] Our simple bowel preparation regimen with no dietary restrictions only requires 4 equivalent split doses of PEG and water, and it enabled the volume of bowel preparation to be significantly reduced to 1.45 ± 0.07 L, which is almost equivalent to a standard CS bowel preparation regimen, while still maintaining a very high excretion rate of 93.9% (31/33) and an acceptable cleansing level.[16] Another key factor that contributed to the high excretion rate in our study could be castor oil, which has been reported to be useful for a high excretion rate and reduced bowel preparation in dialysis patients by promoting catharsis of the intestine.[27, 28] Regarding acceptability, patients tended to prefer CCE-2 with our bowel preparation regimen instead of CS as a monitoring tool, as seen in our questionnaire results. In addition to the reduction of the volume of bowel preparation, its simplicity was favored and enabled the procedure to be performed easily outside the hospital basis. In fact, patients only had to stay inside the hospital for 50 (30–194) minutes in this study, which simultaneously reduced the workloads of the medical personnel. We

have developed and are currently using a system to make the process more patient-friendly by getting the patients to mail the devices back from home.

This is the first study evaluating factors associated with colonic transit time of CCE-2 in UC. Predicting colonic transit time is extremely important in clinical practice because longer transit time may result in a lower excretion rate and acceptability. There was great variability in colonic transit time, from 8 to 489 minutes among the patients who completed CCE-2, and active endoscopic disease was identified as a factor predicting longer colonic transit time. One possible explanation for this is the decreased colonic motility due to inflammation. CCE-2 videos showed that the flow of the capsule slowed down where edema and ulcers presented in the inflamed area, resulting in prolonged colonic transit times, whereas capsules were able to pass normally through the noninflammatory area. Based on the results in our study, patients who seem to have endoscopically active disease may not be suitable candidates for CCE-2 in clinical practice because evaluation of the entire colon may become incomplete, and acceptance may not be high. The excretion rate achieved in this study is much higher than previous studies; however, it is crucial to achieve capsule excretion without fail in order to replace CS as a practical monitoring tool. In addition, it should be noted that CCE-2 cannot replace CS as a method of differential diagnosis or colitis-associated cancer/dysplasia screening because of its incapability to obtain biopsy samples.

There were some limitations in our study, including a limited sample size and being conducted in a single center. Another limitation is a lack of direct comparison between the endoscopic findings of CCE-2 and CS in this study. However, it has been previously confirmed that CCE-2 can be an alternative to conventional CS in determining disease severity of UC,[11, 14, 15] and more importantly, our study demonstrated that endoscopic severity graded by CCE-2 was highly concordant with FC, which suggests that disease activity seemed to be very accurately assessed in this study.[29, 30] With regards to patient recruitment, we did not specifically recruit patients who had refused CS and been scheduled to undergo CCE-2 instead, but merely proposed CCE-2 as an option for monitoring disease activity in UC. However, we cannot thoroughly exclude the possibility that there were some patients who were recruited because of their bias against CS. This might have resulted in some overestimation of the acceptability of CCE-2. In addition, the acceptability of CCE-2 was compared only with previous experience of CS in this study and lack of CS as a control, which is also a limitation. However, most of the patients' CS were performed by the highly skilled endoscopists designated for UC patients in our center, so the acceptability may still be considered high.

In summary, we proposed a simple bowel preparation regimen for CCE-2 in UC patients, which successfully achieved a high excretion rate and acceptance. Therefore, there is potential for its use as the standard regimen in UC, although its validation is still needed. We propose that the most appropriate use of CCE-2 might be as a monitoring tool for UC patients in clinical remission or with minimal disease activity because of the higher excretion rate and cleansing level and more favorable acceptance in such patients.

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