Evaluating mucosal healing using colon capsule endoscopy predicts outcome in patients with ulcerative colitis in clinical remission

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Abstract

AIM
To examine whether second generation of colon capsule endoscopy (CCE-2) is acceptable for assessing the severity of mucosal inflammation and evaluating mucosal healing using CCE-2 is able to predict outcome in ulcerative colitis (UC) patients, especially in clinical remission.

METHODS
A total of 30 consecutive UC patients in clinical remission were enrolled to undergo CCE-2. Clinical remission was defined as clinical activity index (CAI) $\leq 4$ according to Rahmilewitz index. The rate of total colon observation and colon cleansing level were evaluated. Severity of mucosal inflammation in UC was assessed according to the Mayo endoscopic subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Relapse-free survival was assessed. Acceptability of CCE-2 was assessed using a questionnaire survey.

RESULTS
The rate of total colon observation within its battery life was 93.3%. The proportion of "excellent" plus "good" cleansing level was 73.3%. The rate of mucosal healing (MES 0, 1) assessed by CCE-2 was 77.0%. The relapse-free survival rate was significantly higher in MES 0, 1 than in MES 2, 3 ($P = 0.0435$), and in UCEIS 0-3 than in UCEIS 4-8 ($P = 0.0211$), whereas there was no significant difference between CAI 0 and CAI 1-4 groups. A questionnaire survey revealed an overall acceptability of CCE.

CONCLUSION
CCE-2 is acceptable for assessing the severity of mucosal inflammation in UC patients, especially in clinical remission. Evaluating mucosal healing using CCE-2 was able to predict outcome.

Key words: Colon capsule endoscopy; Ulcerative colitis; Mucosal healing; Mayo endoscopic subscore; Ulcerative Colitis Endoscopic Index of Severity

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Core tip: Although mucosal healing is a newly established therapeutic goal in ulcerative colitis (UC), it remains unclear whether evaluating endoscopic activity using colon capsule endoscopy (CCE-2) is able to predict outcome. The present study was a prospective study to evaluate the usefulness of CCE-2 in patients with UC, especially in clinical remission. We revealed that our reduced-volume preparation regimen for CCE-2 could attain a high rate of total colon observation and high acceptability, and that assessment of endoscopic activity by CCE-2 using Mayo endoscopic subscore and Ulcerative Colitis Endoscopic Index of Severity can predict outcome.

INTRODUCTION
Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease with a relapsing and remitting course, and is associated with impaired quality of life[1]. Conventional colonoscopy (CS) plays a major role in the diagnosis and assessment of disease severity and extent as well as surveillance for dysplasia in patients with UC[2-4]. In recent years, besides symptom control, mucosal healing has been established as a new therapeutic goal. It predicts clinical remission and the requirement for hospitalization and surgery[5-8]. However, conventional CS has several limitations, including adverse events, low patient compliance and has manpower restrictions[9,10]. Therefore, an alternative approach that can overcome these limitations is required.

In 2009, the second generation of colon capsule endoscopy (CCE-2) was released, providing a larger number of images per second and a broader viewing angle[11]. CCE-2 has several benefits for patients with UC in assessing mucosal inflammation as the procedure is relatively non-invasive without direct trauma to the mucosa or air insufflation[12,13]. Therefore, it has a high level of patient acceptance without anaesthesia. To date, the accuracy of CCE-2 for assessment of mucosal inflammation in UC appears to be comparable with that of CS[14-16]. However, there have been a limited number of studies. It remains unclear which UC patients may benefit from the use of CCE-2.

The Mayo endoscopic subscore (MES) is widely used in clinical trials to describe the degree of endoscopic activity in patients with UC. In clinical trials as well as in practise, a MES of 0 or 1 is a commonly accepted criterion for mucosal healing and predicts a better outcome[17-19]. More recently, another score index, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), was validated to measure endoscopic severity in UC[20,21]. UCEIS is more sensitive in detecting mucosal inflammation and is superior to other scoring systems in detecting treatment response and predicting disease outcomes[22,23]. However, it is not yet confirmed whether assessment of mucosal inflammation by CCE-2 using
Table 1 Schedule of bowel preparation

| Day       | Diet                                            | Procedure                                      |
|-----------|-------------------------------------------------|-----------------------------------------------|
| Previous  | Low-fibre diet                                   |                                               |
| day       | After dinner 09:00                               |                                               |
| Examination| Magnesium citrate 50 g/180 mL + Sennoside 48 mg | Low-volume PEG (MoviPrep) + 0.5 L water
|           | Mosapride citrate 20 mg                          | Swallowing of CCE-2 capsule                   |
|           | Boosters                                         |                                               |
| Booster (1)| 1 L of low-volume PEG (MoviPrep) + 0.5 L water |                                               |
| Booster (2)| 1 L of low-volume PEG (MoviPrep) + 0.5 L water |                                               |
| Booster (3)| Magnesium Citrate 50 g/180 mL                   |                                               |

MES or UCEIS is able to predict outcome in clinical practise.

Conventional bowel preparations may be excessive for patients with severe or fulminant UC, leading to increased diarrhea and bleeding. Therefore, the preparation should be tailored to the patient in such cases. In the present study, we developed a novel reduced-volume regimen for CCE-2 examination in patients with UC, especially those in clinical remission, and assessed the feasibility of evaluating the severity of mucosal inflammation. Furthermore, we examined whether evaluation of endoscopic activity by CCE-2 using MES and UCEIS was able to predict outcome.

**MATERIALS AND METHODS**

**Study design**

This was a single-center, prospective study conducted in UC patients with clinical remission, carried out in accordance with the Declaration of Helsinki. Approval for the study was obtained from the ethics committee of Hamamatsu University School of Medicine, Japan. Written informed consent for participation in the study was obtained from all patients. This study was registered with the University Hospital Medical Information Network (UMIN), UMIN000030539.

Enrolment of patients aged 16 to 80 years began in October 2015 and was completed in December 2017. Eligible patients had a histologically confirmed diagnosis of UC with clinical remission (Rachmilewitz index ≤ 4) \(^{(24)}\). Patients with the following criteria were excluded: dysphagia; pregnant or possibly pregnant women; a pacemaker or other implanted electromedical device; presence or history of small and large bowel obstruction; a contraindication to bowel preparation (congestive heart failure, renal insufficiency, life-threatening condition); allergic to polyethylene glycol (PEG), magnesium citrate, sennosides, metoclopramide or mosapride citrate; those undergoing magnetic resonance imaging 2 wk after CCE-2; and inappropriate for this study by other reasons judged by the investigators.

**CCE-2 procedure**

The present study used a CCE-2 known as PillCam COLON 2 (Medtronic Japan Co., Ltd., Tokyo, Japan). A modified regimen of bowel preparation was developed to improve patient’s acceptability by reducing the volume and shortening the time of examination using low-volume PEG (MoviPrep, EA Pharma, Tokyo, Japan). Details of the CCE-2 procedure are presented in Table 1. On the day before the capsule procedure, patients ate a low-fiber diet and drank 50 g of magnesium citrate mixed with 180 mL of water and received 48 mg oral sennosides after dinner. On the procedure day, patients swallowed a colon capsule with 20 mg mosapride citrate at 9:00 am. If the capsule had moved out from the stomach to the duodenum, 1 L of low-volume PEG plus 0.5 L of water was administrated as a first booster. After 1 h, 1 L of low-volume PEG plus 0.5 L of water was administrated again as a second booster. Three hours later, if the capsule was not excreted outside the body, 50 g of magnesium citrate mixed with 180 mL of water was administrated as a third booster. Optional use of bisacodyl suppository was allowed only if the capsule was not excreted outside the body after a third booster. Recording was continued until the battery ran down or the capsule was excreted.

**CCE-2 evaluation**

The rate of CCE-2 excretion was calculated, and the transit time for each part of the gastrointestinal tract was recorded. The level of colonic cleansing was scored according to a four-point grading scale, as previously reported \(^{(25)}\). The hepatic flexure and splenic flexure which had been automatically determined by the software were reconfirmed and used as markers to separate the segment in the colon. Each segment was scored as cecum, ascending colon, transverse colon, proximal left-sided colon and distal left-sided colon. Representative images are shown in Figure 1A. Adverse effects were also recorded. CCE-2 images were reviewed independently by two experts of capsule endoscopy (Osawa S and Takano R). One (Osawa S) had eight years of clinical experience in capsule endoscopy (Osawa S and Takano R). One (Osawa S) had eight years of clinical experience in capsule endoscopy and the other (Takano R) had four years of clinical experience, and both had read more than 200 capsule endoscopy videos. The final reports involving endoscopic activity score and cleansing effectiveness were prospectively made based on a consensus bet-
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Table 2  Patients' characteristics n (%)

| Numbers of patients | 30 |
|---------------------|----|
| Gender (male/female) | 18/12 |
| Age [mean ± SD (range), yr] | 48.6 ± 13.3 (24-67) |
| Disease duration [mean ± SD (range), yr] | 13.9 ± 9.5 (1-32) |
| Inpatient/outpatient | 0/30 |
| History of abdominal surgery | 2 (6.7) |
| Type of disease | |
| Total colitis | 19 (63.3) |
| Left-sided | 10 (33.3) |
| Proctitis | 1 (3.3) |
| Disease activity (Rachmilewitz index) | |
| CAI = 0 | 19 (63.3) |
| CAI = 1 | 4 (13.3) |
| CAI = 2 | 4 (13.3) |
| CAI = 3 | 2 (6.7) |
| CAI = 4 | 1 (3.3) |
| Serum albumin (mean ± SD, g/dL) | 4.2 ± 0.5 |
| Serum CRP (mean ± SD, mg/dL) | 0.11 ± 0.15 |

Table 3  Performance of second generation of colon capsule endoscopy procedure

| Total colon observation1, % | 93.3% (28/30) |
| Excretion within 8 h, % | 90.0% (27/30) |
| Capsule retention rate, % | 0% (0/30) |
| Mean transit time ± SD (range), min | |
| Stomach | 27.2 ± 15.4 (4-63) |
| Small intestine | 72.7 ± 34.3 (23-155) |
| Colon2 | 163.9 ± 211.0 (9-775) |
| Cecum and ascending colon | 50.4 ± 84.2 (1-386) |
| Transverse colon | 11.7 ± 17.6 (5-80) |
| Left-side colon | 101.9 ± 186.3 (5-751) |
| Total time2 | 263.8 ± 228.2 (54-952) |
| Total liquid volume of the examination day | 2329 ± 854 (500-3180) |

1Excretion before the battery ran down; 2Involving the end point of battery time without excretion.

CAI: Clinical activity index; 5-ASA: 5-aminosalicylic acid; SD: Standard deviation; CRP: C-reactive protein; CCE: Colon capsule endoscopy.

RESULTS

Patient characteristics

A total of 30 patients were enrolled in the study. Patients' demographics are shown in Table 2. The mean age was 48.6 ± 13.3 years; 18 subjects were male and 12 were female. The mean disease duration was 13.9 ± 9.5 years, and the clinical UC activity of the enrolled patients assessed by Rachmilewitz index was 0.73 ± 1.14 (63.3% in CAI = 0 and 36.7% in CAI = 1-4).

Regarding types of disease, 19 patients (63.3%) had total colitis, 10 (33.3%) had left-sided colitis and one (3.3%) had proctitis. Most of the patients were treated with 5-aminosalicylate drugs. The median observational period was 20.5 mo (range 5-27 mo).

Performance of CCE-2

CCE-2 performance is shown in Table 3. The rate of total colon observation within its battery life in UC patients was 93.3% and 27 patients (90.0%) excreted the CCE-2 within 8 h. The mean total transit time was 263.8 ± 228.2 min (range 54-952 min). The mean colonic and small intestinal transit times were 163.9 ± 211.0 min (range 9-775 min) and 72.7 ± 34.3 min (range 23-155 min), respectively. The total liquid volume on the examination day was 2329 ± 854 mL (range 500-3180 mL). No severe adverse events were observed in this study.

The effectiveness of cleansing using our bowel preparation regimen is shown in Figure 1B. The percentages of “excellent” plus “good” were 40% in the cecum, 57% in the ascending colon, 80% in the transverse colon, 77% in the proximal left-sided colon and 70% in the distal left-sided colon. As a whole, the proportion of...
We examined the distribution of endoscopic activity score assessed by CCE-2 in clinical remission. As shown in Figure 2A, the rate of mucosal healing (MES 0, 1) assessed by CCE-2 was 77.0%. When we evaluated the distribution of endoscopic activity score in between CAI 0 and CAI 1-4 groups, statistical difference was observed in the distribution of MES, whereas distribution of UCEIS by CCE-2 was not statistically different in between CAI 0 and CAI 1-4 groups (Figure 2B).

**Assessment of endoscopic scoring by CCE-2 and outcome**

Based on the Kaplan–Meier survival estimator graphs (Figure 3), the overall cumulative relapse-free and exacerbation-free survival rates at 12 mo were 85.2% and 71.2%, respectively. The relapse-free survival rate was significantly higher in MES 0, 1 than in MES 2, 3 (P < 0.05; log-rank test), and in UCEIS 0-3 than in UCEIS 4-8 (P < 0.05; log-rank test). Furthermore, the exacerbation-free survival rate was significantly lower in MES 0, 1 than in MES 2, 3 and UCEIS 0-3 than in UCEIS 4-8 (P < 0.05; log-rank test).
higher in MES 0, 1 than in MES 2, 3 (P < 0.01; log-rank test), and in UCEIS 0-3 than in UCEIS 4-8 (P < 0.01; log-rank test). However, there was no significant difference between clinical activity index (CAI) 0 and CAI 1-4 groups for both survival rates. MES: Mayo endoscopic subscore; CAI: Clinical activity index; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

Satisfactory survey

To evaluate the acceptability of the CCE-2 procedure, we conducted a questionnaire survey about the following five items: physical pain, mental distress, bowel preparation, next examination and overall acceptability. The results are shown in Figure 4. For overall acceptability, the proportion of “excellent” plus “good” was 90%. For physical pain and mental distress, most patients felt almost nothing or nothing at all. In the pre-treatment, patients’ opinion varied regarding the tolerance of bowel preparation. The questionnaire survey showed that 77% of patients would choose CCE-2 rather than CS for future scheduled endoscopies.

DISCUSSION

The present study was a prospective study to evaluate the usefulness of CCE-2 in patients with UC, especially in clinical remission, and revealed the following novel findings: (1) our reduced-volume preparation regimen for CCE-2 could attain a high rate of total colon observation, and high acceptability; and (2) assessment of endoscopic activity by CCE-2 using MES and UCEIS can predict outcome. These results suggested that CCE-2 could be an alternative to endoscopic examination for follow-up of UC, especially in clinical remission.

The current European Society of Gastrointestinal Endoscopy recommendation for CCE preparation is use of 4 L of PEG solution administered as a split-dose (2 L the day before the examination and 2 L before capsule ingestion) combined with oral use of prokinetics, low-
volume sodium phosphate (NaP) boosters\textsuperscript{[26]}. However, most Japanese patients are not able to tolerate it in clinical practice because of the high volume. Although reduced-volume regimens have been reported for UC patients previously\textsuperscript{[14,27]}, there was still room for improvement in terms of cleansing level and rate of total colon observation, Usui \textit{et al}\textsuperscript{[27]} reported that the proportion of “excellent” plus “good” cleansing was approximately 60%. They discussed that a fair level of colonic cleansing was adequate for the evaluation of UC mucosal severity, whereas it is not sufficient for surveying colon polyps. In this study, we developed a novel reduced-volume regimen of bowel preparation for CCE-2 examination in patients with UC, especially in clinical remission expecting receptive improvement without bowel preparation before swallowing a capsule endoscopy on the examination day. As a result, a shortened transit time through the stomach and colon, and high rates of total colon observation with adequate cleansing could be obtained. More recently, Okabayashi \textit{et al}\textsuperscript{[28]} reported a simple 1-d CCE-2 procedure using castor oil added to the booster without dietary restrictions, which successfully achieved a high excretion rate of 93.9% (31/33) and high acceptance. It is attractive regimen enabled the volume of bowel preparation to be reduced to 1.45 ± 0.07 L whereas the cleansing level was lower than our procedure.

In this study, the rate of mucosal healing assessed by CCE-2 seemed to be equivalent to that of CS. First-generation CCE (CCE-1) displayed a sensitivity and specificity of 89% and 75%, respectively, for the diagnosis of active UC. Although the procedure was safe, the usefulness of CCE-1 for evaluation of UC activity was controversial among studies because of its low specificity\textsuperscript{[14,29-32]}. CCE-2 equipped with an accelerated frame rate and larger angle of view has improved the accuracy for detecting intraluminal abnormality. Oliva \textit{et al}\textsuperscript{[30]} investigated the performance of CCE-2 in 29 paediatric UC patients, and reported that the sensitivity, specificity, positive predictive value and negative predictive value for inflammation detection were 95%, 100%, 100% and 85%, respectively. A recent prospective study in 150 patients revealed that CCE-2 had a sensitivity of 97% and 94% to detect mucosal inflammation (MES ≥ 1) and moderate to severe inflammation (MES ≥ 2), respectively. To detect moderate-to-severe mucosal inflammation, the negative predictive value was improved substantially from 65% with the first-generation capsule to 96% with CCE-2\textsuperscript{[16]}. These studies using CCE-2 support our findings of high detectability using CCE-2.

Until now, there has not been an established scoring system of CCE used worldwide for evaluating endoscopic activity of UC\textsuperscript{[12]}. Recently, the largest-scale study consisting of 150 patients using CCE-2 showed substantial agreement between CCE-2 and CS for either MES [intraclass correlation coefficient (ICC) 0.69; 95% confidence interval (CI), 0.46–0.81] or UCEIS (ICC 0.64; 95% CI: 0.38–0.78) with almost perfect (ICC > 0.80) intra- and inter-observer agreement\textsuperscript{[14]}. However, there have been no studies evaluating whether score of capsule endoscopic activity contributes to the prediction of the clinical course in patients with UC. In our study, assessing mucosal healing by CCE-2 using MES, which is most frequently used in clinical trials and practice, was able to predict outcome in the same way as CS. That is, so-called mucosal healing of MES 0-1 was significantly associated with low relapse-free survival rate and exacerbation rate. Furthermore, we also revealed that UCEIS, which has been validated to be more sensitive in detecting mucosal inflammation, was able to predict outcome in the same way as CS. In this score the threshold for mucosal healing has yet to be determined. Remission is defined as UCEIS 0-1 in some studies\textsuperscript{[12,23,39]}. According to our analysis, MES 0-1 by CCE-2 was equivalent to UCEIS 0-3.

There were several limitations to this study. First, since this study was designed as a preliminary study, a small number of patients were enrolled. Second, this study was conducted in a single center setting that might have involved some bias for selecting patients and the details of the CCE-2 procedure. Third, as all of the enrolled patients were Japanese, it is not confirmed whether bowel preparation regimen of this study is suitable for patients with UC worldwide. Fourth, there was no direct comparison between CCE-2 and CS findings in our study, by which the value of this study would be further increased. Finally, although endoscopic surveillance for colitis-associated cancer is another important issue in the management of UC, the end points of this study did not involve this as it requires tissue sampling for histology.

Nevertheless, despite the limitations and disadvantages of tissue sampling for histology, our study strongly suggests, even in small sample size, that CCE-2 with our regimen of bowel preparation showed high acceptability in UC patients and endoscopic activity by CCE-2 using MES and UCEIS was significantly associated with outcome in clinical remission. This painless, much less invasive tool may be routinely used instead of CS in the near future to monitor inflammation in UC patients, especially those in clinical remission.

**ARTICLE HIGHLIGHTS**

**Research background**

Mucosal healing is a newly established therapeutic goal in ulcerative colitis (UC). The accuracy of the second generation of colon capsule endoscopy (CCE-2) for assessment of mucosal inflammation in UC appears to be comparable with that of colonoscopy (CS). It remains unclear which UC patients may benefit from the use of CCE-2, and whether evaluating endoscopic activity using CCE-2 is able to predict outcome. Further, a standard preparation regimen validated for UC patients in clinical remission has not been established.

**Research motivation**

Conventional CS has several limitations, such as adverse events and low patient compliance. To clarify the usefulness of less-invasive CCE-2 would
provide a new option in clinical practice in UC patients.

**Research objectives**
To assess the feasibility of CCE-2 with a novel reduced-volume regimen in patients with UC in clinical remission, and to examine whether evaluation of endoscopic activity by CCE-2 is able to predict outcome.

**Research methods**
The study was conducted as single-center, prospective setting. A total of 30 consecutive patients were enrolled. CCE-2 performance was evaluated, and acceptability was assessed using a questionnaire survey. Endoscopic activity was assessed according to both Mayo endoscopic subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and its size is expected to be conducted to spread this novel modality widely.

**Research results**
The rate of total colon observation was 93.3% and the proportion of “excellent” plus “good” cleansing level was 73.3% with the reduced-volume regimen. The relapse-free survival rate was significantly correlated with MES and UCEIS, whereas it was not correlated with clinical activity index. A questionnaire survey revealed an overall acceptability of CCE-2.

**Research conclusions**
CCE-2 was acceptable for UC patients in clinical remission. Evaluating mucosal healing using CCE-2 was able to predict outcome.

**Research perspectives**
Despite the small sample size, this study certainly suggested the usefulness of CCE-2 in UC patients in clinical remission. CCE-2 could serve as an alternative modality to CS for follow up of UC. Further extensive study with a larger sample size is expected to be conducted to spread this novel modality widely.
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