

ORIGINAL ARTICLE

Usefulness of ultrasonographic evaluation of stool and/or gas distribution for the treatment strategy of chronic constipation

Noriaki Manabe,*¹ Tomoari Kamada,[†] Hiroaki Kusunoki,[‡] Jiro Hata[§] and Ken Haruma[¶]

*Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, [†]Department of Health Care Medicine, [¶]Department of General Internal Medicine 2, Kawasaki Medical School General Medical Center, Okayama, [‡]Department of Health Care Medicine and [§]Division of Endoscopy and Ultrasonography, Department of Laboratory Medicine, Kawasaki Medical School, Kurashiki, Japan

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Correspondence

Noriaki Manabe, Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School General Medical Center, 2-6-1, Nakasange, Kita-ku, Okayama 700-8505, Japan.
Email: n_manabe@hkg.odn.ne.jp

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Author contribution: Noriaki Manabe designed the study concept and design, analyzed and interpreted the data, and drafted the manuscript. Tomoari Kamada, Hiroaki Kusunoki, Jiro Hata, and Ken Haruma acquired the data and participated in the discussion. All authors participated in drafting or revising the article and approved the final version for submission.

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Abstract

Background and Aim: This study aimed to evaluate the capability of ultrasonography to predict favorable outcomes of various medical therapies in patients with chronic constipation.

Methods: We enrolled 223 patients with chronic constipation (75 men, 148 women; mean age 62.9 ± 3.4 years). Transverse diameters of four segments of the colon (ascending [A], transverse [T], descending [D], sigmoid [S]), and the rectum [R]) were measured. The patients' stool and/or gas distribution was evaluated using the constipation index (CI) $([A + T + D + S + R]/5)$ and the left/right distribution ratio $([D + S]/[A + T])$ according to our previous study. Patients were first treated with fiber- or osmosis-based laxatives for 2 weeks. When constipation was not alleviated, stimulant-based laxatives were added, and the patients were followed for another 2 weeks.

Results: Based on their clinical courses, patients were divided into four groups: non-responders (group A) or responders (group B) to fiber- or osmosis-based laxatives; nonresponders to any medical therapy (group C); and responders to stimulant-based laxatives (group D). The CI was significantly higher in group A than group B ($P < 0.05$), with the receiver operating characteristic (ROC) curve analysis showing a CI cut-off of 21.2 for predicting favorable outcomes of either fiber- or osmosis-based laxatives ($P < 0.05$). Left/right distribution ratio was significantly lower in group C than group D ($P < 0.05$), and the ROC curve analysis showed a left/right cut-off of 0.5 for predicting responders to stimulant-based laxatives ($P < 0.05$).

Conclusion: These findings could help physicians predict favorable outcomes with laxatives without side effects for this patient population.

Introduction

Constipation is a syndrome defined by abnormal bowel symptoms that may be primary or secondary to an underlying disorder.¹ After excluding organic disease, strictures, and evacuation disorders, the treatment of constipation is typically based on single or combined treatment with fiber-,^{2,3} osmosis-,⁴ and/or stimulant-based⁵ laxatives—to which many patients respond. Practitioners have several choices for treating chronic constipation. Patient responsiveness, however, is based on trial and error with the medications. In addition, side effects, such as abdominal pain, sometimes occur because the pathophysiology of chronic constipation varies.⁶

Assessing the colonic transit time (CTT) is important in patients with symptoms of colonic dysmotility because it can provide useful mechanistic insights and gauge the treatment response.⁷ Recently, we developed an ultrasonographic method to evaluate stool and/or gas distribution, which is an indirect indicator of the CTT.⁸ The aim of this study was to evaluate the capability of this method to predict favorable outcomes prior to initiating medical therapy in patients with chronic constipation.

Methods

Subjects. We enrolled 223 patients with chronic constipation (75 men, 148 women; mean age 62.9 ± 3.4 years), which had been diagnosed by the presence of Rome IV-positive, constipation-predominant irritable bowel syndrome (IBS) or functional constipation. Patients continued to take whatever low, stable doses of thyroid replacement, estrogen replacement, low-dose aspirin, birth control pills or depot estrogen injections, and selective serotonin reuptake inhibitor antidepressants they were currently prescribed—but not tricyclic agents. Exclusion criteria included the presence of an organic disease that might explain the patients' symptoms; use of any medication for IBS or bowel dysfunction (within 7 days before the study and throughout the study); and any structural or metabolic disease that affects the gastrointestinal system, including diabetes. Informed consent was obtained from all subjects. The experiment adhered to the tenets of the Declaration of Helsinki and was approved by our institutional ethics committee.

Methods. Figure 1 shows a flowchart of this observational study. According to our previous study,⁸ after an overnight fast, all subjects underwent ultrasonography (US) in the supine position the next morning. The data were then assessed according to the modified algorithm for treating patients with chronic idiopathic constipation suggested by Wald.⁶ Patients were first treated with either a fiber- or an osmosis-based laxative (up to 2.0 g of magnesium oxide daily) for 2 weeks. If patients did not have a dietary fiber intake of more than 15 g per day, they were instructed to increase the amount to a maximum of 25 g per day. The additional fiber was provided in their food, including vegetables, cereals, fruits, wholemeal bread, and brown rice. When constipation was not alleviated despite those 2 weeks of treatment, stimulant-based laxatives (12–24 mg of sennoside tablets in the evening) were additionally prescribed, and the patients were followed for another 2 weeks. This laxative was administered daily

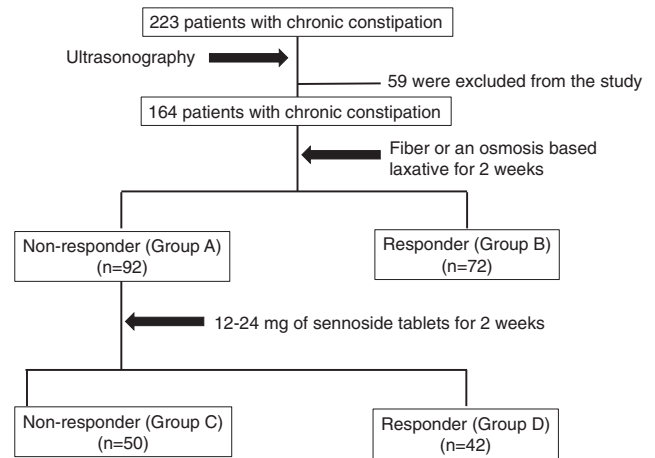


Figure 1 Flowchart of this observational study.

until its efficacy could be judged (by a successful bowel movement). After confirming its efficacy, it was administered “as needed”. The efficacy of either fiber- or osmosis-based laxatives was judged according to (i) spontaneous bowel movements more than twice per week during the last week of treatment and (ii) patient satisfaction of >60% on a visual analog scale questionnaire at the end of the second week. The degree of patient satisfaction was determined by a self-administered visual analog scale that we had used in a previous study.⁹ Each patient was asked: Are you satisfied with this treatment? The efficacy of stimulant-based laxatives was judged according to a bowel movement within 1 day after taking a stimulant-based laxative.

US procedure. Two physicians (Noriaki Manabe, Jiro Hata) performed the US, each blinded to the patients' symptoms at the time. The transverse diameters of each colonic segment (ascending [AC], transverse [TC], descending [DC], and sigmoid [SC] colon and the rectum [R]) were measured using US, and the average value was accepted as the transverse diameter of that segment. Stool and/or gas distributions were evaluated based on three parameters using the following formulas according to our previous study and the constipation index (CI): $(AC + TC + DC + SC + R)/5$; left/right (L/R): $(DC + SC)/(AC + TC)$; and rectal index (RI): R/CI .⁸

Outcome measurements. The primary end-point was whether there were significant differences in US parameters between patients with chronic constipation responding and those not responding to each medical therapy. The secondary end-point was the ability to establish a cut-off value that predicted favorable outcomes prior to initiating medical therapy in patients with chronic constipation.

Statistical analysis. Data are expressed as means \pm standard deviation. The Mann–Whitney U test was used to compare two independent groups. A value of $P < 0.05$ was considered to indicate statistical significance. Cut-offs for US parameters for predicting favorable outcomes of any treatment were obtained from receiver operating characteristic (ROC) curve analyses

Table 1 Patients' characteristics

	Group A (n = 92)	Group B (n = 72)	Group C (n = 50)	Group D (n = 42)
Gender (male/female)	31/61	24/48	14/36	17/25
Mean age (years)	64.5 ± 5.1	63.1 ± 2.3	66.3 ± 4.2	62.4 ± 5.8
Body mass index (kg/m ²)	25.4 ± 2.4	25.5 ± 1.0	24.3 ± 1.8	26.7 ± 3.1

performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a modified version of R commander designed to add statistical functions frequently used in biostatistics (R Foundation for Statistical Computing, Vienna, Austria). Other statistical processing was conducted using SPSS Statistical Package version 17.0 (IBM, Armonk, NY, USA).

The study was approved by the Ethics Committee of the Kawasaki Medical School and conformed to the Declaration of Helsinki in 1995 (as revised in Edinburgh in 2000).

Results

Figure 1 shows a flowchart of patient disposition. Among the 223 patients with chronic constipation who we initially enrolled, 59 were excluded from the study because they did not follow the protocol: 39 patients did not return to the hospital for follow-up, and 20 purchased over-the-counter drugs for constipation. Finally, 164 patients with chronic constipation (55 men, 109 women; mean age 63.9 ± 4.4 years) were analyzed. Patients' characteristics are shown in the Table 1. Their initial US parameters were as follows: CI 19.2 ± 8.5; L/R 0.43 ± 0.34; RI 0.6 ± 0.4. None of them suffered any severe side effects after treatment, such as severe abdominal pain, severe diarrhea, and/or ischemic colitis, although 3 patients in group D (7.1%) experienced mild abdominal pain after we added a stimulant-based laxative and another 50 continued to suffer unrelieved constipation even after being prescribed a fiber- or osmosis-based laxative or a stimulant-based laxative.

Based on the effectiveness of the fiber- or osmosis-based laxatives, the patients were classified into two groups:

92 nonresponders to either fiber- or osmosis-based laxatives (group A) and 72 responders (group B). Comparisons of CI, L/R, and RI between groups A and B are shown in Figure 2. The CI is significantly higher in the group A patients than in those in group B, although the L/R and RI were not significantly different between them. ROC curve analysis showed a CI cut-off value of 21.2 (sensitivity 0.91; specificity 0.35; positive predictive value [PPV] 0.60; negative predictive value [NPV] 0.78; area under the curve 0.63; and 95% confidence interval [95% CI] 0.55–0.71) for predicting responders to either fiber- or osmosis-based laxatives ($P < 0.05$) (Fig. 3).

Based on the effectiveness of stimulant-based laxatives in the 92 patients in group A, they were classified into two groups: 50 nonresponders to stimulant-based laxatives (group C) and 42 responders (group D). Comparisons of CI, L/R, and RI between groups C and D are shown in Figure 4. The L/R ratio was significantly lower in group C than in group D, but there were no significant differences between them for the other two US parameters. The ROC curve analysis showed an L/R cut-off value of 0.50 (sensitivity 0.66; specificity 0.47; PPV 0.54; NPV 0.51; area under the curve 0.53; 95% CI 0.44–0.64) for predicting responders to stimulant-based laxatives ($P < 0.05$) (Fig. 5).

Discussion

This study importantly showed that two parameters (CI and L/R) evaluated by US are associated with the responsiveness of chronic constipation patients to medical therapy. It is considered ideal to adapt the treatment strategy according to the pathophysiology of each disease condition. Based on our study results, we

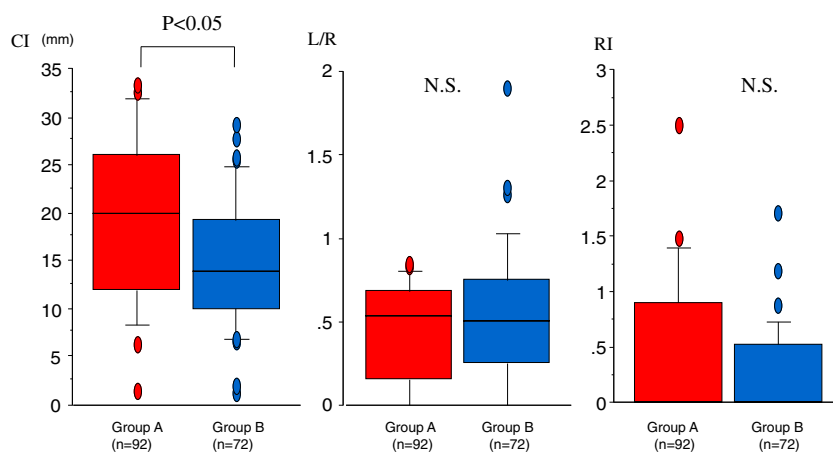


Figure 2 Comparison of the constipation index (CI), left/right distribution ratio (L/R), and rectal index (RI) between nonresponders and responders to either fiber- or osmosis-based laxatives. Group A includes the nonresponders ($n = 92$) and group B the responders ($n = 72$). The CI was significantly higher in group A than in the group B. There were no significant differences between the groups for the other parameters. N.S., not significant.

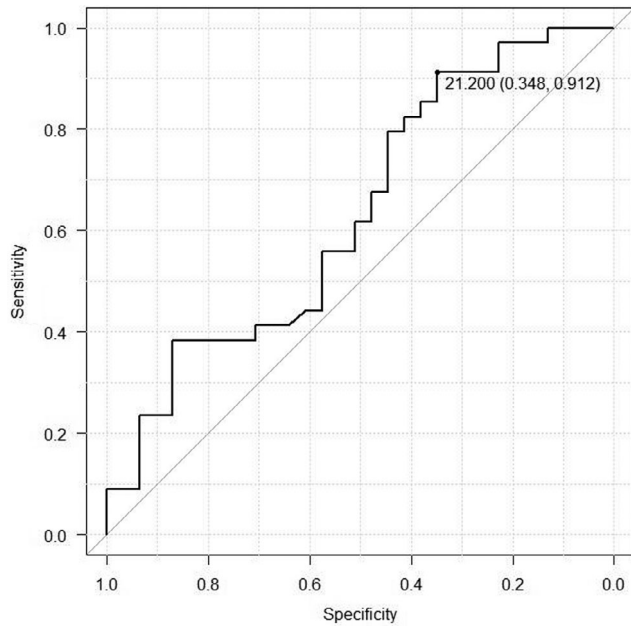


Figure 3 Receiver operating characteristic (ROC) curve analysis produced a cut-off value for the 95% confidence interval (95% confidence interval [CI]) of 21.2 (sensitivity 0.91; specificity 0.35; positive predictive value 0.60; negative predictive value 0.78), area under the ROC curve 0.63, and 95% CI 0.55–0.71 for predicting favorable outcomes of either fiber- or osmosis-based laxatives.

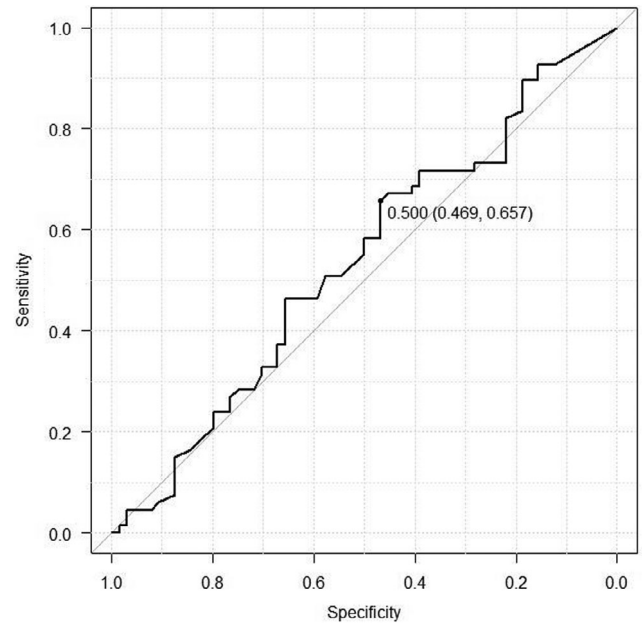


Figure 5 Receiver operating characteristic curve analysis produced a cut-off value for left/right distribution ratio of 0.50 (sensitivity 0.66; specificity 0.47; positive predictive value 0.54; negative predictive value 0.51; area under the ROC curve 0.53; 95% confidence interval 0.44–0.64) for predicting nonresponders to stimulant-based laxatives.

could establish an optimal treatment strategy for patients with chronic constipation whose symptoms would be alleviated without any side effects (e.g. severe abdominal pain, severe diarrhea, ischemic colitis) (Fig. 6).

The CI was significantly higher in group A than in group B, which means that the colonic transit of the group A patients was significantly delayed compared with that in group B. As we demonstrated in our previous study,⁸ the CI is

considered an indirect indicator of CTT. Therefore, it is reasonable that the group A patients, who might have delayed CTT, require stimulant-based laxatives to accelerate the CTT. A CI of >21.2 would indicate the need to prescribe stimulant-based laxatives to obtain maximum clinical usefulness and to minimize possible side effects (e.g. severe abdominal pain, severe diarrhea, ischemic colitis) as much as possible.

We also showed that the L/R ratio was significantly lower in patients not responding to stimulant-based laxatives than in

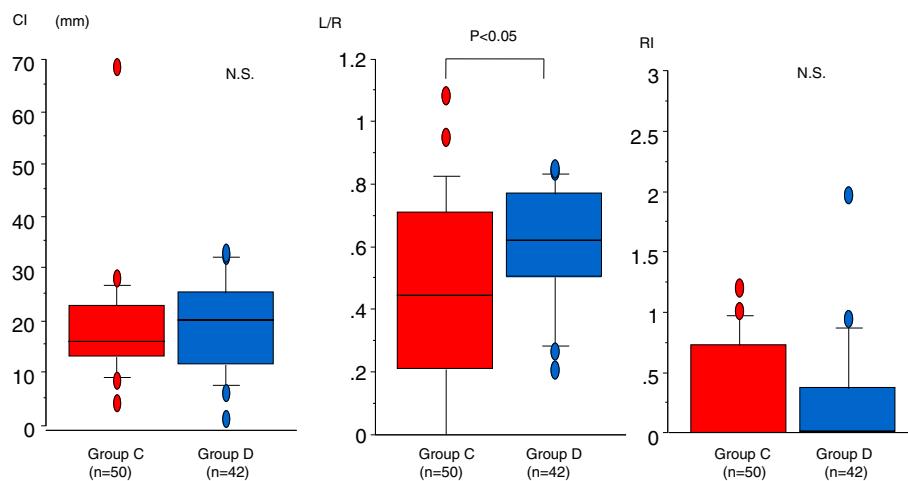


Figure 4 Comparison of constipation index (CI), left/right distribution ratio (L/R), and rectal index (RI) between nonresponders and responders to stimulant-based laxatives. Group C includes the nonresponders ($n = 50$) and group D the responders ($n = 42$). The L/R ratio is significantly lower in group C than in group D.

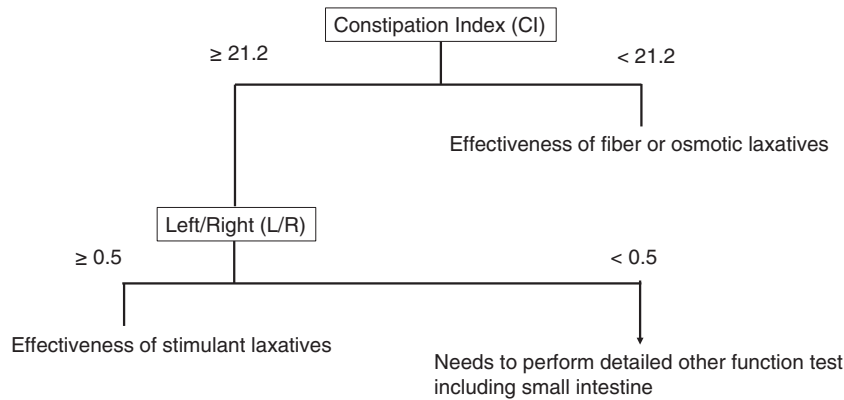


Figure 6 Based on our study results, we established optimal treatment strategies for patients with chronic constipation whose symptoms of chronic constipation were alleviated without side effects (e.g. severe abdominal pain, severe diarrhea, ischemic colitis).

those who did respond. Stivland *et al.*¹⁰ showed that the main transit disorder of patients with severe constipation was characterized by the delayed emptying of the proximal colon. The delay increases the time until fluid absorption in this region is at its highest capacity, thereby leading to the formation of hard stools.¹¹ The CTT thus correlates with stool form as measured by the Bristol Stool Form Scale.¹² Another study showed that the stimulation of transit in the proximal colon is delayed in constipated patients.¹³ As delayed emptying of the proximal colon may lead to proximal colon dilation with gas and stool, the L/R ratio increases. The L/R distribution determined by US is considered an important factor when evaluating the effectiveness of several laxative types based on the patient's pathophysiology. More studies are needed to investigate whether patients' pathophysiology could be applied clinically to determine treatment efficacy *versus* other new classes of constipation therapies, such as secretory drugs.

A recent study demonstrated that the rectal gas volume, determined by abdominal computed tomography imaging, was greater in patients with a rectal evacuation disorder than in those without it,¹⁴ although the criterion of this study was not rectal evacuation disorders but chronic constipation. Other studies have shown that rectal evacuation disorders are the most common cause of refractory chronic constipation.^{15,16} For this study, however, we excluded such patients by taking detailed medical histories and performing physical (including rectal) examinations. Anorectal manometry was performed if deemed necessary. Not all of our study patients underwent anorectal manometry, creating the possibility that a small number of patients with a rectal evacuation disorder might have been included in the study population, especially in group C (the RI tended to be higher in group C patients than in those in group D, although the difference was not statistically significant). We speculated that, if we compared RIs after defecation between patients with a rectal evacuation disorder and those with chronic constipation, there might be a more clear-cut statistically significant difference. We are currently conducting an ongoing study to compare the RI between patients with and without a rectal evacuation disorder.

There are some limitations in this study. First, we did not require the patients to maintain a symptom diary. Therefore, the effectiveness of each treatment was not based mainly on objective indicators but on subjective indicators (i.e. patients'

declarations of symptom alleviation). Further studies using a double-blind design will be necessary. However, patients' outcome measurements were considered important in a recent clinical study on the treatment of patients with functional gastrointestinal diseases, such as chronic constipation.¹⁷ Second, the treatment strategy for patients with L/R < 0.5 (group C) remains unclear in this study. Of the patients in group C, 36 were later treated with secretory drugs (e.g. lubiprostone). Of them, 24 (66.7%) responded, although further studies are needed to clarify this point. Third, the treatment period for this study was 4 weeks, which is considered insufficient because constipation is a chronic disease. In the future, a long-term study to observe the clinical effect of its therapy using this US method will be required.

In conclusion, our data show that two US parameters—CI and the L/R ratio—could reflect the responsiveness of chronic constipation patients to medical therapy. These findings may help physicians predict favorable responses to medical therapies without side effects in this patient population.

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