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Efficacy of Endoscopic Balloon Dilation for Small Bowel Strictures in Patients With Crohn's Disease: A Nationwide, Multi-centre, Open-label, Prospective Cohort Study

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Abstract

Background and Aims: Endoscopic balloon dilation [EBD] is an alternative to surgery for Crohn's strictures. However, there have been no prospective studies of EBD for small bowel strictures in patients with Crohn's disease [CD]. The aim of this study was to clarify the efficacy and safety of EBD using balloon-assisted enteroscopy for small bowel strictures in CD.

Methods: This was a nationwide, multi-centre, open-label, prospective cohort study. The subjects were CD patients with at least one symptom [abdominal pain, abdominal bloating, nausea] attributable to small bowel stricture. The primary endpoint related to short-term outcomes was the level of improvement of symptoms evaluated using a 10-cm visual analogue scale [VAS]. Cases in which VAS scores for all symptoms improved 4 weeks after EBD compared with baseline were considered to have short-term symptomatic improvement. Factors related to short-term treatment outcomes and safety were investigated as secondary endpoints.

Results: A total of 112 patients were enrolled. Seventeen were later excluded because they did not meet the criteria, and the analysis was conducted with the remaining 95 patients. Of these 95 patients, procedure failure occurred in six [6.3%], and short-term symptomatic improvement was achieved in 66 patients [69.5%]. Adverse events were seen in five patients [5%] and all of these improved with conservative treatment. A large dilation diameter of the balloon was a factor contributing to the success of EBD.
Conclusions: EBD using balloon-assisted enteroscopy for small bowel strictures in CD patients was shown to be an effective and safe procedure.
Clinical trial registry: UMIN000005946

Key Words: Crohn's disease; endoscopic balloon dilation; small bowel strictures

1. Introduction

Crohn's disease [CD] is thought to be a chronic inflammatory bowel disease [IBD] characterized by a disabling course because of intestinal tract damage that accumulates gradually with repeated flares and remissions.[1] Chronic progressive inflammation results in the need for surgery in a majority of patients.[2–5] Anti-tumour necrosis factor-α [TNF-α] antibodies can lead not only to the disappearance of symptoms, but also to mucosal healing [MH].[6,7]

Several reports have shown that cumulative surgery rates have been decreasing with the spread of immunomodulators, anti-TNF-α antibodies and other agents.[8,9] Two randomized, controlled trials, on the other hand, indicated no decrease in steroid-free remission or surgery with early introduction of immunomodulators in comparison with conventional treatment.[10,11]

Intestinal strictures are a major cause of surgery in CD and are of two main types: those with oedema due to active CD lesions, and those with fibrotic changes without active lesions.[12] For the latter, low-invasive treatments that do not involve bowel resection, such as endoscopic balloon dilation [EBD] and strictureplasty,[13,14] are sometimes selected. EBD is a highly beneficial and safe endoscopic treatment that has been used for strictures in the gastric outlet, duodenum, colon and ileo-colonic anastomoses.[15] Because the small intestine has a narrow lumen and is frequently affected by CD lesions, it is where CD patients are most susceptible to strictures. However, EBD was rarely used in the past because of limits to the insertion of an endoscope into the deep portion of the small intestine. In recent years, with the development and spread of balloon-assisted enteroscopy [BAE], including both double-balloon enteroscopy [DBE] and single-balloon enteroscopy, endoscopic diagnosis and treatments for various small bowel diseases have been enabled.[16–18] Consequently, the strategy for using BAE for small bowel stricture has changed. Kroner *et al.* carefully examined small bowel strictures with BAE and reported that, of 71 patients, 16 [23%] had CD, and EBD was performed in 16 [23%] who were diagnosed with benign strictures.[19] Thus, EBD using BAE is becoming more common for small bowel strictures, of which the expectations continue to rise as a treatment for CD.[20] Indeed, several reports have suggested its usefulness and safety. However, all were retrospective cohort studies or case series only,[21–27] and there were no prospective studies. This nationwide, multi-centre, prospective, observational study was conducted to determine the usefulness and safety of EBD using BAE for small bowel strictures in CD patients.

2. Materials and Methods

2.1. Patients

The subjects were CD patients who presented with at least one of the small bowel stricture symptoms of abdominal pain, nausea and abdominal bloating, and who met the indication criteria for EBD. The indications for EBD were small bowel strictures with [1] stricture length ≤ 5 cm, [2] no perforative complications, such as fistula or abscess, [3] no deep active ulcers and [4] no tight bends or strong adhesions. With regard to these conditions, small bowel series, computed tomography [CT], magnetic resonance imaging [MRI], BAE or multiple tests were conducted prior to EBD to confirm stricture sites. Strictures of the large bowel and ileo-colonic anastomoses were excluded from this study. Patients with peritonitis, intestinal perforation, severe liver and renal dysfunction, or heart or respiratory failure, those in whom bowel preparation for BAE was not possible, and those with other conditions for which BAE was unsuitable were excluded.

2.2. Method of endoscopic treatment

Decisions regarding the method of EBD and the endoscopes and other devices used for small bowel strictures were left to the discretion of the physician performing the procedure at each institution. In BAE, an SIF Type-Q260 [Olympus] was used for single-balloon enteroscopy, and an EN-450T5 or EN-580T system [Fujifilm Medical] was used for DBE. This study investigated the outcomes of EBD using a balloon catheter only [CRE balloon catheter, Boston Scientific], when no local steroid injection or stent implantation for the stricture was performed. In patients with multiple strictures, the EBD for the stricture thought to be the main cause of the stricture symptoms was investigated. When there were strictures in two or more locations that were thought to be the causes of the stricture symptoms, EBD for all suspected strictures was included in the investigation. EBD for assessment was generally performed only once, and graded dilation was not done.

2.3. Efficacy objectives and assessments

2.3.1. Study design

This study was carried out as a project study of the Study Group on Intractable Diseases, Health and Labor Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan. It was an open-label, multi-centre, prospective cohort study. Twenty-eight institutions in Japan with experience performing BAE participated in the study. Patients who were judged to fulfil the criteria at each institution were enrolled at the study registration centre before BAE and EBD were performed. Case sheets recording short- and long-term outcomes were submitted by the principal investigator at each institution after EBD, at 4 weeks after EBD for short-term outcomes, and 1 and 2 years after EBD for long-term outcomes. This study was registered with the University Hospital Medical Information Network [UMIN], and a study summary, registration status and progress status have been reported [UMIN000005946].

2.3.2. Outcome of endoscopic balloon dilation

The primary endpoint related to short-term outcomes was the level of improvement in symptoms after treatment. Symptoms were evaluated using a 10-cm visual analogue scale [VAS]. Patients completed VAS scores for the three stricture symptoms of abdominal pain, abdominal bloating and nausea at baseline and 4 weeks after EBD. The VAS scores were completed without a doctor or nurse present. From these three results, cases in which all VAS scores decreased after 4 weeks compared with baseline were considered to have short-term symptomatic improvement. However, cases when there was no change from baseline in one of the VAS scores after treatment [including cases with a VAS score at baseline of 0] were considered to have short-term symptomatic improvement if the other VAS scores decreased. The definition of short-term outcome was not taken into consideration for the degree of improvement of each VAS score. With this definition, all other cases were judged as unsuccessful short-term treatment. Technical success was defined as successful inflation of a balloon catheter for the small bowel stricture. In other words, cases in which EBD could not be performed were taken to be procedural failure. Secondary endpoints were successful endoscopic passage through the stricture after EBD, the level of improvement in each VAS score after treatment and the frequency of complications. Patients who required surgery or intensification of treatment during the 4 weeks after EBD, which was the time point for evaluating short-term treatment efficacy, were taken to be cases of unsuccessful short-term symptomatic improvement. To identify the factors for treatment success, a comparison was made of patients' baseline characteristics, stricture status and factors related to therapeutic procedures in cases of short-term symptomatic improvement and unsuccessful ones.

For long-term treatment outcomes, the primary endpoint was the rate of surgery after EBD, and the secondary endpoint was the rate of repeat EBD. Both rates were investigated based on 2-year follow-up.

2.4. Ethical considerations

Ethics reviews for this study were performed at all participating institutions. Subjects received full explanations from their primary physicians, using prescribed written information, on the methods for BAE and EBD, complications and how they would be dealt with, the confidentiality of personal information, and the content of this study. A written, informed consent form was then completed and submitted to the respective institution.

2.5. Statistical analysis

Statistical analysis was done using SPSS version 20.0 [IBM Statistics]. Continuous variables are expressed as means ± standard deviations. A *t*-test was used to compare differences between mean values. The chi-squared test or Fisher's exact test was used to compare frequencies. A p-value < 0.05 was considered significant.

3. Results

3.1. Patient enrolment

Patient enrolment in this study is shown in Figure 1. A total of 112 patients from 23 institutions were enrolled during the period from August 2011 to October 2013. After this, 11 patients who were found to be unsuitable on imaging tests were excluded. BAE was not performed in one patient even though that patient was enrolled. There was also one patient in whom BAE was performed after enrolment, but whose stricture was found to be mild on endoscopic observation, and dilation was judged unnecessary. Data could not be analysed in another four patients: three whose VAS scores were not obtained and one who could not complete the VAS because of a psychiatric disorder. After excluding these patients, the remaining 95 were the subjects for analysis in this study. Table 1 shows the baseline characteristics and concomitant treatments of subjects at the time EBD was performed. The mean age at the time of EBD was 38.5 ± 10.4 years, disease duration was 11.1 ± 8.8 years and disease location was L1 in 59 patients [62.1%] and L3 in 36 patients [37.9%]. Fifty-eight patients [61.1%] had a history of previous surgery. Forty-four patients [46.3%] were using anti-TNF-α antibodies, and 42 [44.2%] were using immunomodulators.

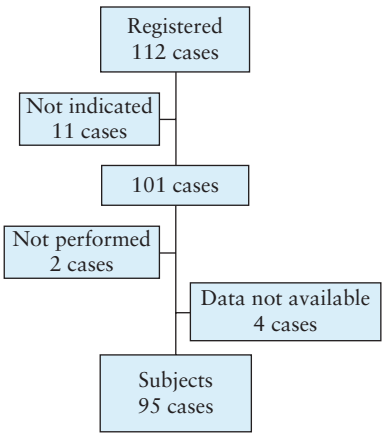

Figure 1 Enrolment in the study. A total of 112 eligible patients were registered; 95 patients who met the inclusion criteria made up the study group.

3.2. Short-term treatment outcomes

The details of the small bowel strictures in this study are also shown in Table 1. The strictures were located at 74 naïve sites [77.1%], while only 22 occurred at anastomotic sites [22.9%]. Forty-six patients [48.4%] had a single stricture, and 49 patients [51.6%] had multiple strictures, including a mild stricture that did not need EBD. There were multiple lesions causing the stricture symptoms in only one patient, who had suspected lesions at two sites, the ileum and an ileal–ileal anastomosis. The most common stricture length was less than 3 cm at 82 locations [85.4%], while stricture length was ≥ 3 cm at only nine locations [9.4%].

EBD was successful in 89 [93.7%] of the 95 subjects. The main reasons for procedure failure were contraindications to EBD due to active deep ulcers in three cases and internal fistula in one case. The other reasons were inability to reach the stricture site and inability to identify the lumen at the stricture site in one case each. Using the definition of success in this study, 66 cases [69.5%] were considered to have short-term symptomatic improvement. Successful endoscopic passage through the stricture after EBD was achieved in 73 subjects [76.8%]. Of the six procedure failure cases within 4 weeks after EBD, which was the period for investigation of short-term outcomes, one patient underwent surgery. Of the 23 patients for whom EBD was judged to be unsuccessful even though the procedure was a success, none underwent surgery within 4 weeks. Hence, surgery was performed within 4 weeks in only one patient. The other 94 patients were the subjects for investigation of long-term outcomes [Figure 2].

The VAS score for abdominal pain had decreased significantly [p < 0.0001] at 4 weeks after EBD compared with baseline [Figure 3a]. VAS scores for abdominal bloating and nausea also

Table 1. Baseline characteristics, concomitant treatments and details of the stricture sites of the subjects at the time of initial endoscopic balloon dilation

Characteristic		Location of stricture*	*n* = 95
Gender [M:F]	66:29	Naïve site	74 [77.1%]
		Jejunum	4
Age [mean ± SD, years]	38.5 ± 10.4	Ileum	70
		Anastomotic site†	22 [22.9%]
Disease duration [mean ± SD, years]	11.1 ± 8.8		
		Number of strictures	
History of surgery [yes/no]	58/37	Single	46 [48.4%]
		Multiple	49 [51.6%]
Disease location [L /L3]‡	59/36	2	22
		3	11
Concomitant treatments§		4 or more	16
Anti-TNF-α antibody [yes/no]	44/51	Stricture length	
		<3 cm	82 [85.4%]
Steroid [yes/no]	2 / 93	≥3cm	9 [9.4%]
		N/A¶	5
Immunomodulator [yes/no]	42 / 53		
		Prestenotic dilatation	
Enteral nutrition** [yes/no]	25 /70	Presence	66 [68.8%]
		Absence	30 [31.2%]

TNF, tumour necrosis factor.
*One patient who had two main strictures was included.
†Ileo-colonic anastomotic sites were not included.
‡Disease location was described according to the Montreal classification.
§Patients who received two or three treatments were included.
**Patients who received 900 kcal/day or more of enteral nutrition were included.

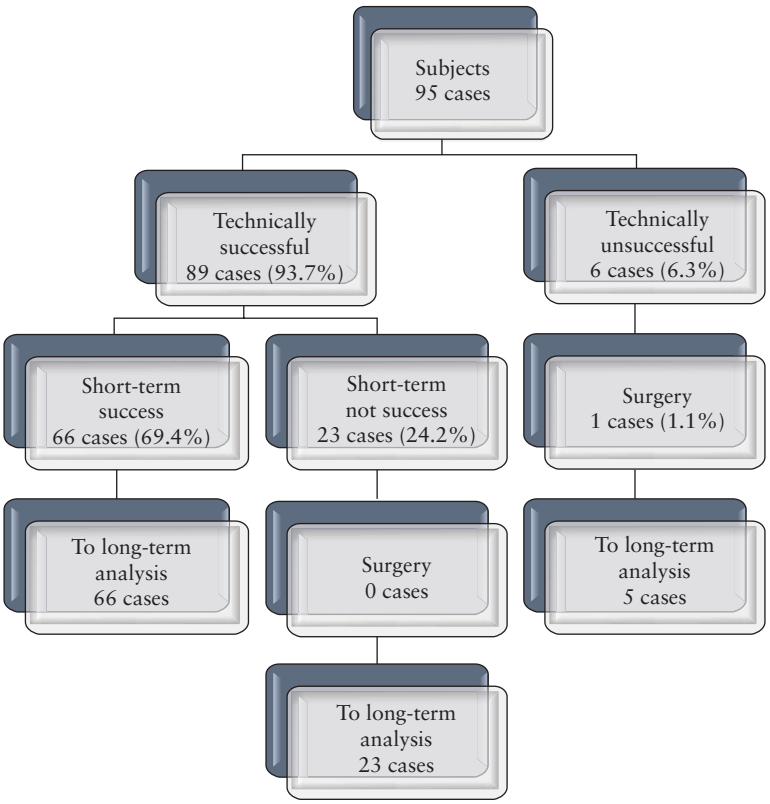

Figure 2. Short-term outcomes of endoscopic balloon dilation [EBD]. Of the 95 cases, procedural failure occurred in six [6.3%], and short-term symptomatic improvement was achieved in 66 patients [69.5%] according to the definition of the study protocol. Surgery was performed within 4 weeks in only one patient in the short-term no symptomatic improvement group.

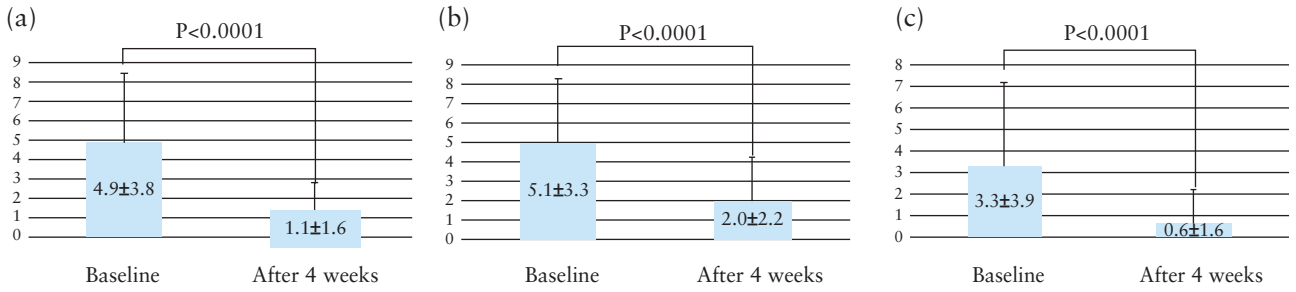

Figure 3. VAS scores. [a] The VAS score for abdominal pain is significantly lower at 4 weeks after EBD than at baseline [$p < 0.0001$]. [b] The VAS score for abdominal bloating is significantly lower at 4 weeks after EBD than at baseline [$p < 0.0001$]. [c] The VAS score for nausea is significantly lower at 4 weeks after EBD than at baseline [$p < 0.0001$].

decreased significantly [$p < 0.0001$] at 4 weeks after EBD compared with baseline [Figure 3b, c].

3.3. Comparison of factors related to short-term outcomes with EBD

Various factors were compared in the 66 subjects in the short-term symptomatic improvement group and the 23 subjects in the no improvement group, but no clear differences were seen in patients' baseline characteristics, stricture site or length, or number of strictures [Table 2]. In a comparison of dilation techniques, the dilation diameter of the balloon was significantly larger in the short-term symptomatic improvement group than in the no improvement group [15.20 ± 1.70 mm vs 13.65 ± 2.59 mm, $p = 0.03$]. Patients in whom the scope passed successfully thorough the stricture tended to show short-term symptomatic improvement compared to patients without this success [$p = 0.078$]. In addition, 8- to 10-mm balloon catheters were used significantly more often in the short-term symptomatic no improvement group [$p = 0.03$] [Table 3].

3.4. Safety profile

Adverse events were seen in five patients [5%]. Bleeding at the stricture site was observed in three patients. Transfusion was required in one of these patients, and endoscopic haemostasis [clipping] was required in another. Haematoma formation at the stricture site was seen in one patient. Localized peritonitis occurred in one patient. These complications were resolved by conservative therapies, such as short-term fasting and antibiotics. There were no cases of death or surgery due to complications.

4. Discussion

Endoscopic treatments for intestinal strictures in CD help avoid surgery, but treatment remains challenging for clinicians. Especially for small bowel lesions before the advent of BAE, it was impossible not only to perform the EBD but also simply to observe the lesions. In recent years, EBD has been triedusing BAE, but there is no clear evidence for its usefulness. To the best of our knowledge, this is the first multi-centre, prospective clinical study of small bowel strictures in CD. Of the 95 subjects, EBD was technically successful in 89 [93.7%], which is equivalent to the outcomes for EBD in the large bowel and ileo-colonic anastomoses.[15,28] Because of the anatomical characteristics of the small intestine, insertion of the endoscope to the stricture site and holding it in place and ensuring the visual field while EBD is performed are thought to be more difficult than with colonoscopy. However, it was demonstrated that there are no disadvantages in terms of technical problems. Clear standards for judging the short-term effect of EBD are lacking, and disappearance of symptoms, passage of an endoscope and VAS scores following EBD have been used.[12,15,24,28] Although successful endoscopic passage through the stricture was the clearest endpoint for EBD, there was a concern that the operator would try to insert a scope forcibly to achieve short-term success. Despott *et al.* also reported on the efficacy of EBD using VAS scores in a prospective case series.[24] Therefore, with regard to safety, the VAS score was chosen to evaluate the short-term efficacy of EBD in the present study. However, this might be the limiting evaluation method because the definition using VAS score for EBD was not a standardised method.

To exclude secondary symptoms from BAE and EBD in the present study, VAS scores were evaluated at 4 weeks rather than soon after EBD. Judgments were also made using VAS scores for the three stricture symptoms of abdominal pain, abdominal bloating and nausea. According to these evaluations, there was short-term success in 66 patients [69.5%]. Compared with previously reported outcomes of EBD for small bowel stricture, the procedure failure rate was about the same.[21,23–27,29] The method of evaluating short-term clinical efficacy differs by report, but it was also very similar, and no perforation from the procedure was seen [Table 4].[21,23–27,29] This prospective, comparative, observational study with a large number of patients demonstrated the efficacy and safety of EBD for small bowel stricture.

In a comparison of cases in which EBD was successful and unsuccessful, there were no clear significant differences in baseline characteristics or stricture length or severity. In some reports, longer stricture length was found to be a risk factor related to EBD success.[15,25] In the present study, however, no specific risk factors could be identified. Among the various factors related to endoscopic technique in EBD, dilation diameter was significantly larger in the successful group than in the short-term symptomatic improvement group. This suggests that an effective diameter of about 15 mm is needed for improvement of stricture symptoms.

As CD is a chronic relapsing inflammatory disease, control of disease activity via drug therapy and improvement of quality of life are crucial. Anti-TNF-α antibody therapy is very effective in CD, resulting in disappearance of symptoms, avoidance of long-term hospitalization and surgery, and MH.[6,7,30] At the same time, however, intestinal strictures are known to occur during treatment with anti-TNF-α antibodies.[31,32] In this study, 46.3% of the subjects were treated with anti-TNF-α antibodies. However, whether anti-TNF-α antibody treatment was used did not affect the short-term outcome of EBD. Although intestinal strictures may occur at a certain frequency with anti-TNF-α antibodies, the present study suggests that surgery can be avoided by performing EBD, as in cases we have reported previously.[33]

Table 2. Comparison of baseline characteristics and concomitant treatments between patients with and without short-term symptomatic improvement

	Total cases [*n* = 89]	With short-term symptomatic improvement [*n* = 66]	Without short-term symptomatic improvement [*n* = 23]	*p* value
Characteristics				
Sex [M:F]	62:27	46:20	16:7	0.80
Age [mean ± SD, years]	38.6 ± 10.6	38.2 ± 10.9	39.7 ± 10.0	0.53
Disease duration [mean ± SD, years]	11.1 ± 8.9	9.9 ± 7.9	14.3 ± 11.0	0.09
History of surgery [yes/no]	53/36	38/28	15/8	0.70
Disease site [ileitis/ileo-colitis]	55/34	43/23	12/11	0.32
Concomitant treatments*				
Anti-TNF-α antibody [yes/no]	43/46	30/36	13/10	0.36
Steroid [yes/no]	2/87	1/65	1/22	0.45
Immunomodulator [yes/no]	39/50	31/35	8/15	0.34
Enteral nutrition† [yes/no]	35/54	23/43	12/11	0.14

TNF, tumour necrosis factor.
*Patients who received two or more treatments were included.
†Patients who received 600 kcal/day or more of enteral nutrition were included.

Table 3. Comparison of details of stricture site and EBD technique-related factors between patients with and without short-term symptomatic improvement

	Total cases [*n* = 89]	With short-term symptomatic improvement [*n* = 66]	Without short-term symptomatic improvement [*n* = 23]	*p* value
Stricture site				
Location*				
Naïve lesion	69	52	17	0.94
Anastomotic lesion	21	15	6	
Number				
Single	43	32	11	0.97
Multiple	46	34	12	
Width*				
<5 mm	54	42	12	0.7
5–10 mm	33	23	10	
>10 mm	3	2	1	
Length [mm, mean ± SD]†	1.31 ± 0.80	1.33 ± 0.82	1.25 ± 0.78	0.68
EBD technique-related factors				
Scope [DBE/SBE]	60/29	42/24	5/18/2017	0.3
Balloon catheter size [mm]				
8–10	6	2	4	0.03
12–15	54	45	9	0.04
15–18	23	17	9	0.34
18–20	4	3	1	1
Dilation size [mean ± SD, mm]‡	14.86 ± 2.01	15.20 ± 1.70	13.65 ± 2.59	0.03
Balloon pressure [mean ± SD, atm]	6.32 ± 2.41	6.61 ± 2.22	5.50 ± 2.88	0.1
Technical success [yes/no]	74/15	58/8	16/7	0.083

EBD, endoscopic balloon dilation; DBE, double-balloon enteroscopy; SBE, single-balloon enteroscopy; TNF, tumour necrosis factor.
*One patient who had two main strictures was included.
†Data not available in four cases.
‡Data not available in 11 cases.

This study has several limitations. First is the bias in patient selection. The subjects in this study were a selected cohort. For example, surgery is usually selected and EBD is not selected for long, advanced strictures of over 5 cm, strictures with fistulas or strictures with multiple narrow spots in the small bowel. The fact that this study examined treatment outcomes with EBD for small bowel strictures in the absence of these conditions is probably its biggest limitation. Second, to clarify the usefulness of EBD for small bowel stricture as a means of eliminating stricture, it should preferably be compared with surgery. Several such reports exist, but they were all small-scale, retrospective, cohort studies.[34,35] The usefulness of these two interventions should be investigated in a randomized, controlled study. However, the degrees of patient invasiveness of surgery and EBD differ greatly, and from an ethical viewpoint, studies that assign subjects to the two procedures are problematic. For the present study, therefore, a prospective, open-label design was selected. Third, the EBD techniques, including selection of devices and dilation pressure settings, were left to the discretion of the endoscopists at the institutions participating in this study. As a result, they were not consistent between institutions. However, the institutions participating in

Table 4. Summary of published studies on endoscopic balloon dilation using balloon-assisted enteroscopy for small bowel stricture in Crohn's disease

Author, year	Number of subjects	Study design	Procedure failure [%]	Short-term clinical efficacy* [%]	Perforation [%]
Fukumoto *et al*., 2007 [21]	23†	Retrospective cohort	NA‡	74	0
Ohymiya *et al*., 2009 [23]	16‡	Retrospective cohort	4	NA	NA
Despott *et al*., 2009 [24]	11	Prospective case series	27	73	9
Hirai *et al*., 2010 [25]	25	Retrospective cohort	28	72	0
Gill *et al*., 2014 [29]	10	Retrospective cohort	0	80	20
Hirai *et al*., 2014 [25]	65	Retrospective cohort	20	80	2
Sunada *et al*., 2016 [27]	85	Retrospective cohort	NA	87	5
Current study	95	Prospective cohort	6	70	0

*According to definition based on each study.
†Included patients with Crohn's disease only.
‡Data not available.

this study belonged to a nationwide study group on IBD in Japan, and experts in IBD and small bowel endoscopy were in charge of the treatments. Consequently, there were no large differences in the various issues related to endoscopic technique and procedure due to institutional differences. Finally, the subjects included patients with small bowel strictures in multiple locations. There is no absolute proof that the stricture for which EBD was performed was the lesion responsible for symptoms, but improvement in all of the stricture symptoms [abdominal pain, abdominal bloating and nausea] was the primary endpoint for the short-term success rate, and reliability is thought to be high.

In conclusion, this was the first prospective study of EBD for small bowel strictures, and the results suggest that: the technical feasibility is equivalent to that of conventional EBD for the large bowel and for ileocolic anastomoses; short-term symptomatic improvement was seen in 70% of the subjects; and the procedure is safe. EBD was shown to contribute to the elimination of patients' stricture symptoms. In the technical investigation of EBD, a diameter of about 15 mm was shown to be preferable. When small bowel strictures are seen in CD patients, EBD with BAE is effective if the criteria for its use are met, and it is one of the low-invasive treatments that should be tried before resorting to surgery.

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Conflict of Interest

None.

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Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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