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ORIGINAL ARTICLE

Efficacy and Safety of Endoscopic Balloon Dilation for Upper Gastrointestinal Strictures of Crohn's Disease

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Abstract
Background Few articles focused on endoscopic balloon dilation (EBD) in the management of Crohn's strictures in the upper gastrointestinal (GI) tract.
Aims The purpose of this study was to evaluate the long-term efficacy and safety of EBD for Crohn's strictures in the upper GI tract and to determine early predictors of response and surgical intervention.
Methods All eligible patients who underwent EBD for Crohn's strictures in the upper GI tract were retrospectively reviewed. The long-term success was defined as the recovery of normal diets without surgical intervention over the follow-up period. In order to seek early predictors, patients who achieved long-term success were compared with those who didn't.
Results A total of 67 dilations of upper GI strictures were performed between June 2011 and March 2015 on 24 patients (mean age 25.6 ± 6.7, 20 male) with Crohn's disease. Technical success was achieved in 62 of 67 dilations (92.5 %) with a complication rate of 3 %. After the median follow-up period of 23.0 months (range 6.2–51.2 months), nine patients underwent surgical intervention, nine patients were still depending on tube feeding; in the meantime, only six (25 %) patients achieved long-term success. Additionally, patients who remained 1 month intervention-free (55.6 vs. 5.9 %, $P = 0.015$) were more likely to achieve long-term success.
Conclusions EBD was a safe procedure, but not a potent therapy for Crohn's upper GI strictures. Meanwhile, 1-month response could serve as an early predictor of the long-term response.

Keywords Endoscopic balloon dilation · Crohn's disease · Upper gastrointestinal strictures · Early predictors

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Introduction

Crohn's disease (CD) is a chronic inflammatory disorder, which can affect any part of the gastrointestinal (GI) tract. Gottlieb and Alpert reported the first case of upper GI involvement in 1937 [1]. Since then, the upper GI CD has been increasingly recognized [2]. The incidence reported varies between 0.5 and 4 % when clinical symptoms and radiographic examinations are used for diagnosis, and the majority of patients in this subgroup manifest obstructive symptoms, especially in the advanced period [3, 4].

The management of Crohn's strictures has been challenging. Available medical treatments not only work poorly when fibrotic strictures formed, but they also play a limited role in preventing the fibrogenic process [5, 6]. Surgical intervention is effective, but it is associated with markedly increased morbidity and carries a high rate of reoperation [7–9]. So, a fresh therapy characterized by obstruction relief and surgery avoidance is considerably required.

Endoscopic balloon dilation (EBD), a minimally invasive and bowel conserving therapy, has exhibited advantages in lower GI strictures of CD [10–16]. However, only five reports of 13 cases have specially discussed EBD for the upper GI strictures of CD [17–21]. In the light of insufficient data, the efficacy and safety of EBD for CD-associated upper GI strictures remain uncertain. On the other hand, a recent study reported that salvage surgery after failure of EBD increased postoperative complications when compared with surgery first [22]. That is to say, for some patients, not only do subsequent dilations not prevent surgical intervention, they even affect surgical outcomes. Therefore if we could find early predictors, timely converting EBD to surgical intervention, patients would benefit most. Hence the aim of this study was to evaluate the long-term efficacy and safety of EBD in the management of Crohn's upper GI strictures and to determine early predictors of long-term response.

Patients and Methods

Patients

This was a retrospective study and was approved by the Institutional Review Board of Jinling Hospital. Patients who underwent EBD for CD-associated upper GI strictures in our inflammatory bowel disease (IBD) center and had a follow-up period of more than 6 months after the initial dilation were included in this study.

The inpatient and outpatient electronic medical records of all eligible patients were carefully reviewed. Their demographics, disease onset and evolution, strictures characteristics and dilation course, concomitant medications and post-dilation follow-up data were collected. Some patients were also contacted to inquire about their current food intake type (orally or by feeding tubes) and dilation satisfaction.

Endoscopic Procedure

The indications for EBD for upper GI strictures in CD patients at our institution are as follows: (1) upper GI strictures causing obstructive symptoms which is refractory to conventional medical therapy, (2) length of stricture shorter than 4 cm, and (3) no associated fistula or abscess connected to the stricture. The diagnosis of Crohn's disease was established in accordance with WHO diagnostic criteria. Strictures were confirmed based on the definition in Montreal Classification [23]. Endoscopic biopsy was performed to exclude malignant strictures and other benign non-CD strictures.

Before dilation, we confirmed the site, length and number of the strictures via upper GI contrast or abdominal computed tomography (CT). Every patient gave informed consent at the time of the procedure. All dilations were performed by an experienced endoscopic team in our IBD center under general anaesthesia.

Endoscopic dilation was performed using a Through-The-Scope Boston Scientific balloon (CRE Wire-guided Balloon Dilators; 18 mm diameter, 5.5 cm long; Cork, Ireland), through an Olympus-GIF-H260 endoscopy (9.8 mm diameter; Tokyo, Japan) without fluoroscopic guidance. As all patients in this study had high-grade strictures (not traversable or passage with severe resistance [24]), dilation was performed in an antegrade way. First the endoscopy was advanced into the proximal side of the stricture. Under direct vision, the wire was introduced through the stricture, and then the CRE balloon was threaded over the guide wire. When the balloon was positioned accurately across the stricture, it was gradually inflated to an appropriate size (15, 16.5 or 18 mm) deemed to be safe by the endoscopist. Passage through the stricture was attempted immediately after the dilation and was used to assess technical success. No one was given concomitant intralesional corticosteroid injection.

During and after dilation, patients were closely monitored for signs of excessive bleeding and perforation, with surgery backup ready.

Peri-dilation Management

To make the following outcome measurement clear and easier to understand, we reported the peri-dilation management carried out at our institution as follows.

At admission, all patients were suffering from obstructive symptoms, vomiting, bloating or cramping. Most patients had weight loss, and the serum C-reactive protein (CRP) level or erythrocyte sedimentation rate (ESR) increased in some patients. Endoscopic examination in some patients revealed hyperaemia, oedema or ulcer in stricturing lesions. Therefore, to reduce patients' inflammation and improve their nutrition status, we performed percutaneous endoscopic gastrostomy and jejunostomy (PEG/J) or placed nasogastric and nasojejunal tubes before dilation, with gastrostomy or nasogastric tubes for decompression and jejunostomy or nasojejunal tubes for enteral nutrition (EN) delivery. In patients with distal esophageal strictures, only the nasogastric tube was placed for EN delivery.

After dilation, the gastrostomy or nasogastric tubes were closed, and oral diets were attempted, from fluid to solid food. The first inpatient follow-up was carried out 1 month after the dilation. If patients could tolerate normal diets well, these tubes would be removed. Otherwise, these tubes would be kept in place and additional dilation or surgical intervention would be considered if high-grade strictures existed.

As a result, the absence of these tubes accurately reflected a stable recovery of normal diets and was an indicator of dilation success.

Outcome Measurement

Long-term success, which was defined as the recovery of normal diets without PEG/J, nasogastric or nasojejunal tubes, as well as avoidance of surgical intervention over the follow-up period, was chosen as the primary outcome.

The secondary outcome included technical success, safety, 1-month intervention-free rate, surgery-free survival and additional intervention-free survival. The definitions of the secondary outcome are shown in Table 1. Patients who quit EBD for other therapies without surgical intervention were deemed to have surgical intervention in statistics.

In order to determine early predictors of long-term response, demographics, strictures characteristics and dilation-associated data were analyzed between patients who achieved long-term success and those who didn't.

Statistical Analysis

Continuous variables were calculated as mean with standard deviation (SD) or median with interquartile range (IQR) or range if not distributed normally. Discrete variables were calculated as percentages. Mann–Whitney test was used for unpaired analysis of continuous variables, and Fisher exact test was used for analysis of discrete variables. Kaplan–Meier survival analysis was used to assess the surgery-free or additional intervention-free survival. Analyses were all done by using SPSS v.22 (IBM Analytics, NY, USA). All P were two-sided and $P < 0.05$ was considered statistically significant.

Results

Patient Demographics and Strictures Characteristics

Twenty-four consecutive eligible CD patients (20 males) who underwent endoscopic dilation of upper GI strictures between June 2011 and March 2015 were included. Patients' demographic and clinical characteristics are shown in Table 2. Mean age at CD diagnosis was 21.2 ± 5.3 years. Median interval between diagnosis and upper GI involvement was 3.1 years (IQR, 1.1–4.8 years), and median interval between onset of obstruction symptoms and the first dilation was 0.5 year (IQR, 0.4–1.4 years). Ninety-five percent (95.8 %, 23/24) of patients were on CD-associated medications, with the majority of patients (54.2 %, 13/24) on azathioprine. In addition, 21 patients (87.5 %) were prescribed proton pump inhibitors (PPIs) in combination. CRP was normal and Crohn's disease activity index (CDAI) was below 150 at the first dilation.

All the strictures were primary high-grade strictures, of which 22 strictures (91.7 %) were not traversable. Most strictures (83.3 %) were located in duodenum, with one located in the distal esophagus and three in pylorus. Each patient has only one stricture, and no concurrent strictures or fistulas elsewhere were detected during the follow-up period (Table 3).

Efficacy and Safety of EBD

The long-term outcome of EBD during the median follow-up period of 23.0 months (range, 6.2–51.2 months) is shown in Fig. 1. A total of 67 dilations were performed with a median interval of 1.6 months (IQR, 1.2–4.2 months) between two adjacent dilations. The immediate technical success was obtained in 92.5 % (62/67) of dilations. Median numbers of dilations per patient were 3 (range 1–6), and the median dilation size was 18 mm (IQR, 15–18 mm) (Table 3).

During the duration of the follow-up, six patients (25.0 %) had PEG/J or nasogastric and nasojejunal tubes removed and resumed normal diets (long-term success, primary outcome), of which three patients achieved long-term success after the first dilation and another three after three dilations (Fig. 1). The long-term success has been maintained for the median duration of 20.4 months (rang, 6.5–39.2 months) by the end of the follow-up.

Fifteen patients remained surgery-free until the end of the follow-up. The cumulative rate of surgery-free survival

Table 1 Secondary outcomes of endoscopic balloon dilation

Secondary outcome	Definition
Technical success	Passage of the endoscope through the stricture without resistance immediately after the dilation performed safely
Safety	Any complication associated with endoscopic procedure
One-month intervention-free rate	No additional dilation or surgical dilation needed within 1 month after the initial dilation
Surgery-free survival	The time from the first dilation to surgical intervention
Additional intervention-free survival	The time from the first dilation to the first event of either endoscopic dilation or surgical intervention

Table 2 Patients' demographic and clinical characteristics

Factor	Patients ($N = 24$)
Gender, *n* (M:F)	20:4
Age at diagnosis, mean ± SD, year	21.2 ± 5.3
Age at onset of obstructive symptoms, mean ± SD, year	24.7 ± 6.7
Age at the first dilation, mean ± SD, year	25.6 ± 6.7
Smoking status at the first dilation, *n* (%)	
Never	21 (87.5)
Former	2 (8.3)
Current	1 (4.2)
Symptoms, *n* (%)	
Nausea or vomiting	20 (83.3)
Bloating	13 (54.2)
Anorexia or early satiety	4 (16.7)
Reflux or belching	2 (8.3)
Epigastric pain	3 (12.5)
Weight loss	20 (83.3)
Disease location, *n* (%)	
Upper GI tract (L4) only	1 (4.2)
Upper GI tract (L4) + ileum (L1)	3 (12.5)
Upper GI tract (L4) + ileocolon (L3)	20 (83.3)
History of bowel resection, *n* (%)	6 (25.0)
Feeding tube use at the first dilation, *n* (%)	24 (100 %)
Feeding tube use at the last visit, *n* (%)	9 (37.5)
Concomitant medications during dilation, *n* (%)	
Mesalazine (Pentasa/Etiasa)	5 (4/1) (20.8)
Azathioprine	13 (45.8)
Tripterygium	4 (16.7)
Thalidomide	1 (4.2)
PPIs	21 (87.5)
CRP (>8 mg/l) at admission, *n* (%)[a]	4 (26.7)
CRP (>8 mg/l) at the first dilation, *n* (%)[a]	0 (0)
CDAI (>150) at the first dilation, *n* (%)[a]	0 (0)

GI gastrointestinal, *CRP* C-reactive protein, *CDAI* Crohn's disease activity index

[a] Data not available for all cases. Missing values: CRP at admission = 9, CRP at the first dilation = 6, CDAI at the first dilation = 9

was 64.5 and 56.4 % at 1 and 2 years, respectively (Fig. 2). Nevertheless, nine patients in the surgery-free group were still living on tube feeding after repetitive dilations. None of them were satisfied with the endoscopic dilation. Additional endoscopic dilation or surgical interventions were required in 21 patients (87.5 %) during the entire

Table 3 Characteristics of strictures and endoscopic treatments

Factor	Patients ($N = 24$)
Location of strictures, *n* (%)	
Distal esophagus	1 (4.2)
Pylorus	3 (12.5)
Duodenum	20 (83.3)
The first part	15 (62.5)
Junction of the first and second parts	5 (20.8)
Endoscopic features at the first dilation, *n* (%)	
Hyperaemia and oedema	18 (75.0)
Ulcer and scar	3 (12.5)
Cobblestone	2 (8.3)
No inflammatory presence	3 (12.5)
Degree of stricture, *n* (%)	
Mild or moderate resistance	0 (0)
Severe resistance	2 (8.3)
Pinhole and not traversable	22 (91.7)
Cumulative numbers of dilations	67
Median numbers of dilations (range)	3 (1–6)
Median balloon size[a] (IQR), mm	18 (15–18)
At the first dilation	15 (15–17)
At re-dilations	18 (16–18)

IQR interquartile range

[a] The one who encountered perforation at the first dilation is not included

follow-up period. The additional intervention-free rate dropped to 11.1 % < 1 year after the first dilation (Fig. 2). Sixty- two percent (62.5 %, 15/24) of patients underwent a second endoscopic dilation or a surgical intervention within 1 month after the initial dilation; the 1-month intervention-free rate was 37.5 % (9/24).

Complications occurred during two procedures in two patients, with an overall complication rate of 3.0 % per procedure and 8.3 % per patient. Both patients presented with an acute abdomen secondary to perforation after dilation. One occurred at the first dilation, the other occurred at the second, and both were managed by urgent duodenal repair.

Early Predictors of Long-Term Response

To determine early predictors of long-term response, demographics, strictures characteristics and dilation-associated data were compared between patients with and without long-term success, which is shown in Table 4. Compared with long-term unsuccessful patients, patients with long-term success had shorter disease duration (1.9 vs. 4.6 years, $P = 0.039$). Patients who remained 1-month intervention-free tended to achieve long-term success more often than those who didn't (55.6 vs. 5.9 %, $P = 0.015$). Besides, patients with concomitant medication of triptergium wilfordii Hook. f. (TwHF) were more likely to achieve long-term success than those with other medical therapies (75 vs. 15 %, $P = 0.035$). As CRP available was normal at the initial dilation, no comparison would be made.

Discussion

We reported the largest series on EBD for CD-associated upper GI strictures. We demonstrated the safety of this procedure, but the long-term efficacy was unfavorable. Meanwhile, 1-month response could serve as an early predictor of long-term response.

In this study, we performed a total of 67 dilations. The overall complication rate was 3 % per procedure. The technical success was achieved in 92.5 % of dilations. In the largest series on endoscopic dilation for the lower GI strictures, Van Assche et al. [16] reported a complication rate of 5.1 % and a technical success rate of 97 %, respectively. In a systemic review [12], which included most ileocolonic strictures, the major complication rate was 2 % and the technical success rate was 86 %. Thus EBD for the upper GI strictures was as safe as that for the lower GI strictures. In addition, the low complication rate and the excellent technical success rate were also good proof of our endoscopic skills. Theoretically, it was considered that EBD performed under fluoroscopic guidance was safer, for fluoroscopy helped to identify both the proximal and distal ends of the strictures in case of iatrogenic perforation [25]. However, clinical evidence was insufficient. As a result, we look forward to a prospective study directly assessing the safety of EBD with or without fluoroscopic guidance.

With regard to the long-term efficacy of EBD, we have two expectations, obstruction relief and surgery avoidance. So we defined the long-term efficacy as the recovery of normal diets without surgical interventions, which is similar to the definition of surgery-free survival in other studies [10–16]. As the food intake status after the dilation was observed for at least 1 month, patients with long-term success have a more confirmed recovery of normal diets in our study. By the end of the follow-up, 62.5 % of patients avoided surgery, yet only 25 % of patients resumed normal diets. The remaining patients lived on tube feeding, though more endoscopic dilations have been performed (Fig. 1). Besides, when all dilations were taken together, the median interval between two adjacent dilations in our study was 1.6 months. Though repeat EBD was safe and wouldn't lead to short bowel syndrome, such frequent recurrence and dilations severely affected patients' quality of life. As a result, the long-term efficacy of EBD in the management of

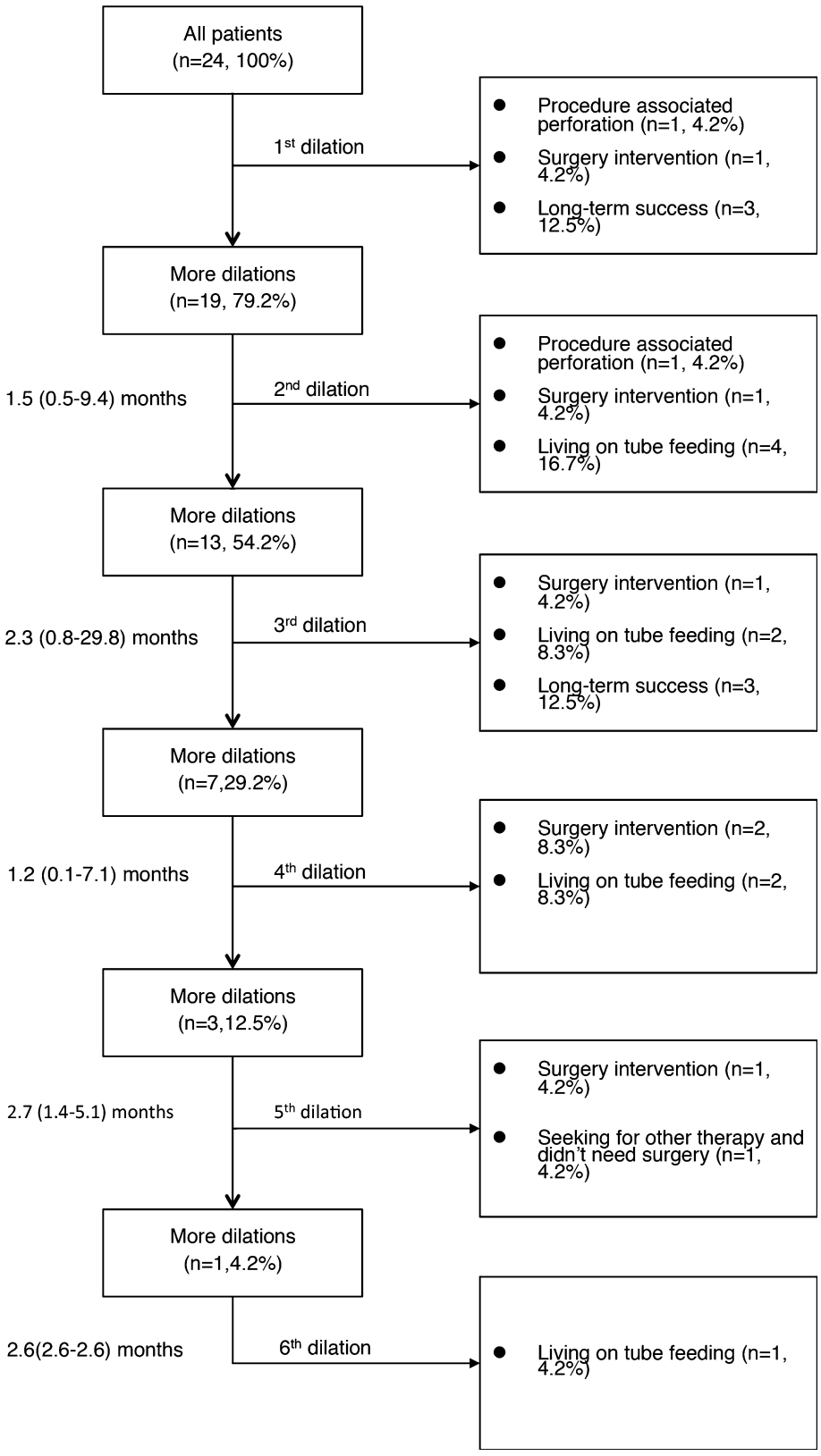

Fig. 1 Flowchart of long-term outcome of endoscopic balloon dilation in the treatment of upper gastrointestinal Crohn's disease strictures. The median interval (range) between two adjacent dilations lies on the *left of the arrow*

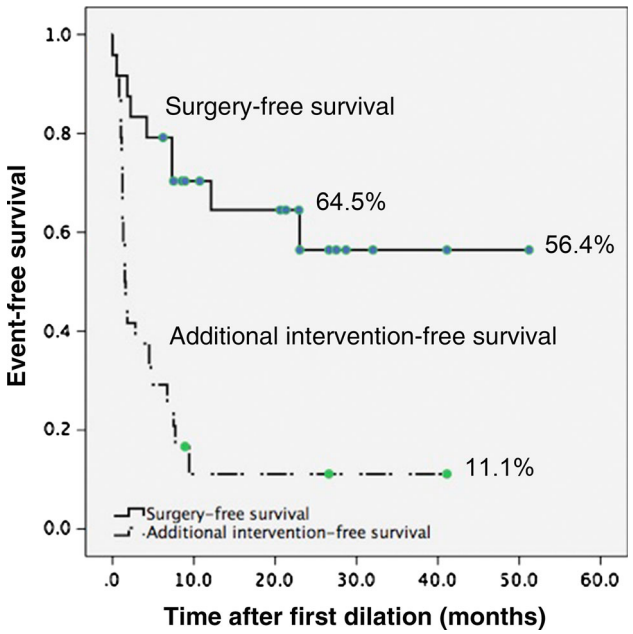

Fig. 2 Surgery-free survival and additional intervention-free survival after initial endoscopic balloon dilation in the management of Crohn's upper gastrointestinal strictures

Crohn's strictures in the upper GI tract was not demonstrated in our study.

A recent study directly compared postoperative outcomes of salvage surgery after failure of EBD with surgery first, with results showing that salvage surgery significantly increased postoperative complications [22]. Nevertheless, in our cases, patients who achieved long-term success did benefit from endoscopic dilation. By the end of the follow-up, they maintained normal diets for the median duration of 20.4 months. Then the question is, who will benefit from subsequent dilations and who should timely turn to surgical intervention? Demographics, strictures characteristics and dilation-associated data were analyzed between patients who achieved long-term success and those who didn't.

Interestingly, we found that patients who didn't need additional intervention within 1 month after the initial dilation were more likely to achieve long-term success (55.6 vs. 5.9 %, $P = 0.015$). We speculated the 1-month response might serve as an early predictor for long-term efficacy of EBD, which could be used to decide whether to repeat dilation or turn to surgical intervention.

Surprisingly, analysis revealed patients on TwHF were more likely to achieve long-term success (75 vs. 15 %, $P = 0.035$). TwHF, for its immunomodulating effect, was used as an effective alternative in our center when guideline-recommended medical treatment failed [26, 27], and recent basic studies have also detected its anti-fibrotic effect in animal models of fibrotic disease [28–31]. Therefore, whether the protective activity of TwHF was due to the immunomodulating effect or anti-fibrotic effect, or both of them, deserved further investigation.

Besides, patients who achieved long-term success have shorter disease duration (1.9 vs. 4.6 years, $P = 0.039$). Fibrosis resulting from chronic inflammation was considered to be the basis of fixed stricture in Crohn's disease [6, 17]. The longer disease duration was reported to

Table 4 Clinical, stricture and dilation characteristics between patients with and without long-term success

Factor	Long-term successful cases ($N = 6$)	Long-term unsuccessful cases ($N = 18$)	*P*-value
Gender (M:F)	6:0	14:4	0.539
Median duration of disease (IQR), year	1.9 (1.7–2.5)	4.6 (3.1–6.7)	**0.039**
Median duration of obstructive symptoms (IQR), year	0.8 (0.5–1.3)	0.5 (0.2–1.4)	0.315
Median age at the first dilation (IQR), year	22.5 (18.9–26.4)	26.8 (20.1–26.8)	0.162
Median duration of follow-up (IQR), year	24.0 (12.0–37.5)	23.0 (11.1–28.4)	0.739
History of bowel resection, *n* (%)	1 (16.7)	5 (27.8)	1.0
Median dilation times (IQR)	2 (1–3)	3 (1–5.2)	0.125
$N > 3$	0 (0)	7 (38.9)	0.130
Concomitant treatment during dilation, *n* (%)			
Mesalazine (yes/no)	1/5	4/14	1.0
Azathioprine (yes/no)	1/5	12/6	0.061
TwHF (yes/no)	3/3	1/17	**0.035**
Thalidomide (yes/no)	1/5	0/18	0.25
PPI (yes/no)	6/0	15/3	0.546
One-month intervention-free (yes/no)	5/1	4/14	**0.015**

IQR interquartile range, *TwHF* tripterygium wilfordii Hook. f

Bold values indicate statistical significance

promote the development of stenosis [32]. Clinically, upper GI strictures can be insidious and silent. The prevalence of gastroduodenal Crohn's disease increases to 40 % if endoscopy is used for diagnosis [33]. Therefore scheduled endoscopic examination should be arranged to detect early the upper GI involvement after the diagnosis of Crohn's disease. Timely medications might postpone inflammation-induced strictures; concomitant PPIs might also be helpful [2].

A big limitation of our study is the small sample size, which weakened the statistic power. What we found in our study needs to be verified in a larger one. However, the clinical incidence of gastroduodenal Crohn's disease is <4 %, so it is difficult to enroll enough patients in one center. Therefore, multicenter cooperation is worthwhile. Furthermore, due to the special management before and after the dilation at our institution, the efficacy of EBD to some extent was affected. We defined the new long-term success, accurately reflecting the efficacy of EBD. Like other studies, our study had no control group. A study directly comparing EBD with surgical interventions in the treatment of shorter upper GI strictures is required.

In conclusion, EBD was a safe procedure, which could be performed repetitively to postpone surgical interventions for Crohn's upper GI strictures, yet the long-term efficacy in ameliorating the obstructive symptoms was weak. One-month response could serve as an early predictor, deciding whether to repeat dilation or turn to surgical intervention in advance.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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