



Initial safety and efficacy of a novel drug-coated balloon for treatment of benign intestinal strictures

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Background and Aims: Intestinal strictures are common adverse events of chronic bowel conditions such as Crohn's disease, diverticulitis, and ulcerative colitis or after intestinal surgery. Mechanical endoscopic balloon dilation (EBD) is the standard-of-care intervention, whereas multiple, repeat EBD therapy is often needed. A novel drug-coated balloon (DCB) was developed to dilate strictures while concurrently delivering medication to reduce the rate of recurrence of strictures. We present the results of a first-in-human, observational, open-label clinical trial in small- and large-bowel strictures.

Methods: Ten human adult subjects with chronic single, discrete, and benign intestinal stricture were treated and followed for 2 years. Outcomes included the Endoscopic Obstructive Score (EOS), Obstructive Symptom Score (OSS), and adverse events.

Results: In the first-in-human trial of benign small- and large-bowel strictures, subjects presented with a mean stricture diameter of 10.3 mm, average EOS of 2.7, and OSS of 25.2. The technical success rate was 90%, and no participants had major treatment-related adverse events. EOS decreased to .2 on average at 6 months. At 2 years, the retreatment-free survival rate was 100% and the average OSS was .6. Subjects tolerated the procedure well.

Conclusions: DCB treatment of benign small- and large-bowel strictures appears to be safe and showed durable results of decreased symptoms and freedom from recurrence through 2 years. Results warrant further investigation in large-scale clinical trials. (Clinical trial registration number: NCT03886324.) (iGIE 2024;3:10-4.)

Intestinal strictures are one of the most common adverse events of chronic bowel conditions such as inflammatory bowel disease (IBD), including Crohn's disease (CD), and ulcerative colitis (UC), diverticulitis, and ischemic colitis or after intestinal surgery (eg, gastric bypass, bowel resection). The management of intestinal strictures often requires surgical resection or surgical stricturoplasty. In a recent meta-analysis comparing surgical approaches with colonic and rectal anastomoses and postoperative outcomes, stricture was reported in 2.52% of patients after surgery, and surgical technique was not predictive of the rate of stricture occurrence.¹ However, surgery is associated with the risk of postoperative adverse events and postoperative disease recurrence, resulting in additional surgical intervention.² Furthermore, strictures are still reported to have a 20% and 49% surgical recurrence rate at 5 and 10 years, respectively, after the initial surgical resection for CD.³⁻⁵

Frequent bowel resection surgery can cause short gut syndrome. Surgical stricturoplasty is an alternative, bowel-sparing procedure that avoids resection and preserves intestinal absorptive capacity. Patients undergoing stricturoplasty are at risk for recurrence that is comparable with patients un-

dergoing resection.⁶ Reoperation for recurrent disease has been reported in 29%, 34%, and 73% of patients after 5, 7.5, and 10 years, respectively.⁷ Approximately 11% of patients experience strictures after initially being diagnosed with CD. The formation of these strictures can be caused by underlying chronic inflammation, postoperative ischemia, or other fibrotic processes.^{4,8} Patients with intestinal strictures typically experience abdominal pain, loss of appetite, fatigue, nausea, bloating, or vomiting.

Restorative proctocolectomy with ileal pouch-anal anastomosis is the preferred surgical approach for patients with medically refractory ulcerative colitis or colitis-associated neoplasia. Ileal pouch strictures are common after reconstruction surgery. The management of pouch stricture can be challenging.^{9,10} For a nonsurgical alternative, endoscopic balloon dilation (EBD) has become an accepted modality for the treatment of IBD-associated strictures.¹¹⁻¹³ The most common methods are through-the-scope balloons. In a systematic review and pooled data analysis of 13 retrospective studies from 1990 to 2007, 58% of patients achieved long-term clinical efficacy (free of surgery) with EBD.¹⁴ However, in a meta-analysis of 25 pooled studies,

80.6% of patients still required repeat dilation 5 years after EBD.¹⁵ Recurrence of strictures after EBD with a mechanical balloon is common.^{16,17}

The ProTractX3 through-the-scope drug-coated balloon (DCB; GIE Medical, Inc, Plymouth, Minn, USA) is the first paclitaxel DCB developed to manage intestinal strictures through mechanical dilation and addresses stricture recurrence through topical drug treatment. Paclitaxel is an antiproliferative drug used extensively in other medical devices to reduce the rate of restenosis in vascular tissue after percutaneous transluminal angioplasty and has been approved by the U.S. Food and Drug Administration for the treatment of fibrotic urethral strictures in men (Urotronic, Plymouth, Minn, USA).¹⁸⁻²⁰ The ProTractX3 DCB is designed to reduce the need for reintervention by depositing paclitaxel during stricture dilation to limit fibrosis and recurrence. Early efficacy and safety of the treatment of benign intestinal strictures with the ProTractX3 DCB were assessed in both a preclinical safety and pharmacokinetic study under Good Laboratory Practices and a first-in-human, single-center, prospective cohort clinical study (the POISE study).

METHODS

Study device

The ProTractX3 DCB is a wire-guided, 3-stage, through-the-scope balloon designed to dilate benign strictures in the GI tract. The distal end of the catheter has a semi-compliant inflatable balloon coated with a proprietary coating with the active pharmaceutical ingredient paclitaxel. The device mechanically dilates the stricture through the operating channel of an endoscope while facilitating the application of paclitaxel. The DCB provides symptomatic relief while limiting fibrotic tissue regrowth in the dilated stricture. The study device is available in 3 sizes, each with 3 diameter stages based on inflation pressure used: 12 mm (12, 13.5, and 15), 15 mm (15, 16.5, and 18), and 18 mm (18, 19, and 20).

Preclinical study design

A preclinical study was performed on 39 healthy male or female pigs. The results of the parallel study of the DCB in benign esophageal strictures have been published.²¹

Clinical study design

The POISE study is a prospective, single-arm, open-label study to assess the safety and efficacy of the ProTractX3 DCB for the treatment of chronic benign intestinal strictures (ClinicalTrials.gov: NCT03886324). Ten subjects between ages 18 and 80 years with single chronic benign intestinal strictures were enrolled at a single site in Paraguay. Chronic strictures were defined as confirmed symptomatic and anatomic recurrence after at least 2 prior EBDs.

Local ethics committee approval was obtained before the initiation of study-specific activities (Ministry of Health

and Ethics Committee, Paraguay, February 13, 2019). Participants were required to provide written informed consent before study-specific activities were conducted.

Treatments were performed in a hospital endoscopic suite with patients under general anesthesia. Depending on the stricture location, the target final diameter was ≥ 12 mm for the small intestine and ≥ 14 mm for the large intestine using the ProTractX3 DCB. To avoid overdilation and multiple dosing, predilation was used with commercially available uncoated balloons before the application of the DCB. This practice allowed safe dilation of tight strictures and ensured adequate dilation above the minimum target diameter using the ProTractX3 DCB. Subjects were followed at 30 days, 3 months, 6 months, 1 year, and 2 years postprocedure.

Subjects between ages 18 and 80 years with at least 2 previous dilation sessions with recurrence of intestinal obstructive symptoms were enrolled. Patients with single, discrete strictures ≤ 4 cm in length with a diameter that did not allow for colonoscope passage were eligible to be enrolled. Subjects were excluded if they had extrinsic benign bowel strictures, malignant strictures, or more than 1 stricture. Additional exclusions were acute bowel obstruction requiring urgent surgical intervention; suspected perforation of the GI tract; distal rectum or anal strictures complicated with abscess, fistula, ulceration, or associated with mesenteric vessel thrombosis; and severe coagulation disorders or other significant comorbidities.

Major efficacy endpoints were technical success (defined as successful delivery, inflation, and withdrawal of the device without major device-related adverse events or device malfunction), proportion of subjects with improvement in the Endoscope Obstruction Score (EOS) at 6 months, percentage of subjects with improvement in the EOS, improvement in obstructive symptoms during follow-up using the Obstructive Symptom Score (OSS), and reintervention-free survival. The EOS is designed to assess the ability of an endoscope to pass through the stricture. It is a 4-grade scale (0-3), with grade 3 being severe resistance to the endoscope or the inability of the endoscope to pass through the stricture.²² We designed and used an OSS for the quantification of symptoms and response to endoscopic therapy. The OSS is a composite questionnaire that combines severity using a 5-point Likert scale (1 = no pain, 2 = mild, 3 = moderate, 4 = severe, 5 = unbearable) and frequency (from 0 = none to 6 = always) of various obstructive symptoms over 14 days. A patient's total OSS consisted of the sum of his or her integrated symptom score (severity of the symptom multiplied by the frequency). The symptoms defined were constipation, crampy abdominal pain, inability to have a bowel movement or pass gas, loss of appetite, and swelling or distention of the abdomen. The primary safety endpoint was the incidence of serious balloon dilation-related adverse events within 30 days postprocedure such as death, perforation, bleeding requiring intervention or transfusion, severe abdominal pain requiring medications, and infection requiring hospitalization or intravenous antibiotics.

Statistical analysis

Sample sizes for the animal studies were estimated based on prior experience using DCB in the urinary tract of pigs and based on the standard deviation of tissue levels of paclitaxel in these studies. Human studies were descriptive given that this was a first-in-human study and no prior data existed. The analysis population for this study was an intention-to-treat population, including those subjects who met eligibility criteria and underwent attempted treatment with the study device. Continuous variables are summarized through descriptive statistics such as mean, standard deviation, and median. Frequency counts and percentages are used to summarize categorical measures.

RESULTS

Ten human subjects were enrolled from February to July 2019. Demographics and baseline characteristics were listed in Table 1. Predilation was conducted with a commercially available 3-stage through-the-scope balloon to an average inflation diameter of 15.5 mm. Three sizes of DCBs were used: 18 × 55 mm in 5 subjects (50%), 15 × 55 mm in 4 (40%), and 12 × 55 mm in 1 (10%). At baseline, subjects had a mean EOS of $2.9 \pm .3$ and an OSS of 25.2 ± 22.4 .

All subjects safely completed the treatment, and no participants experienced a major device or procedure-related adverse event 30 days after the procedure. One adverse event (constipation) was reported among the 10 subjects, with no serious adverse events noted.

Technical success was 90.9% per device analysis and 90.0% per subject analysis. Dilation with the ProTractX3 DCB resulted in an immediate improvement in stricture diameter that was maintained through at least 6 months of follow-up. All 10 subjects exhibited procedural success (≥ 1 point improvement in EOS), with 7 subjects improving from an EOS of 3 (no passage) at baseline to 0 (no resistance). At 6 months after treatment, the mean EOS was $.2 \pm .4$, decreasing by 2.7 from baseline. Furthermore, the EOS for all subjects (100%) was improved by at least 1 grade, with 7 subjects improving by 3 grades and the remaining 3 subjects improving by 2 grades (Fig. 1).

Obstructive symptoms were improved after DCB treatment, and improvements were maintained through 2 years after the procedure. The OSS improved from 25.2 at baseline to .8, 2.5, 1.0, .5, and .6 at 4 weeks, 3 months, 6 months, 1 year, and 2 years, respectively. All subjects experienced an improvement in symptoms from baseline, with an average of a 97.0% improvement in OSS from baseline to 2 years. Symptom improvement was seen across all symptom types (Fig. 2). No subjects required repeat intervention (dilation or surgery) for the treated strictures or experienced a recurrence of their intestinal obstruction through 2 years of follow-up.

TABLE 1. Clinical study demographics and baseline characteristics (n = 10)

Variables	Values
Age, y	50.9 $\pm$ 14.8
Male sex	5 (50.0)
Height, cm	169.2 $\pm$ 9.5
Weight, kg	77.0 $\pm$ 21.2
Body mass index, kg/m ²	26.9 $\pm$ 7.6
Race/ethnicity	
Hispanic or Latino	10 (100)
White	0 (0)
GI stricture-specific medical history	
Diverticulitis	2 (20.0)
Abdominal infection	1 (10.0)
Weight loss	5 (50.0)
Abdominal radiation	1 (10.0)
Abdominal surgery	7 (70.0)
Stricture characteristics	
Length of stricture, cm	.94 $\pm$.6 (11)
Diameter of stricture, mm	10.25 $\pm$ 3.6 (4)
Discrete morphology	11/11 (100.0)
Simple morphology	11/11 (100.0)
Stricture type	
Primary	3 (30.0)
Diverticulitis	2 (20.0)
Peptic	1 (10.0)
Secondary	7 (70)
Gastrojejunal	2 (20)
Coloanal	2 (20)
Colorectal	2 (20)
Unspecified	1 (10)
Stricture location	
Upper GI tract	3 (30.0)
Lower GI	7 (70)
Previous no. of stricture dilations	
No. of previous stricture intervention	2.1 $\pm$.3
Balloon dilations	10 (100)

Variables are mean $\pm$ standard deviation (n), n/N (%), or n (%).

DISCUSSION

The first-in-human POISE study is a prospective, single-arm study to assess the initial safety and efficacy of the ProTractX3 DCB. Results indicate that the ProTractX3 DCB was able to alleviate symptoms caused by intestinal strictures and maintain bowel patency through at least 2 years postprocedure. These results were achieved in a difficult population that had at least 2 prior dilations of the same stricture, with the interval between prior dilation and stricture recurrence leading to the study procedure an average of 79 days.

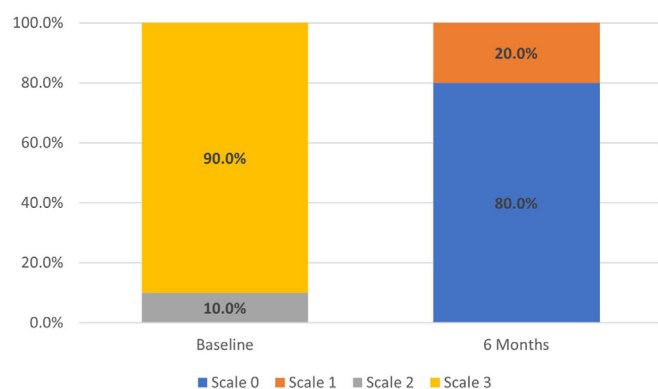


Figure 1. Average Endoscopic Obstruction Score at baseline versus at 6 months.

Endoscopic therapy with mechanical balloons and surgery currently represents the standard of care for intestinal strictures.^{5,23} Surgical therapy, such as bowel resection, is a high-risk procedure associated with developing further adverse events and comorbidities. In addition, postoperative disease recurrence is common, especially in patients with IBD. In contrast, EBD is a popular, effective, and minimally invasive alternative. A pooled analysis of 3213 EBD procedures for CD-associated strictures showed an 89% success rate and 81% improvement in the relief of clinical symptoms. However, 47.5% of patients experienced stricture recurrence after 3 years, with 28.6% requiring future surgical intervention.²⁴ These statistics illustrate the capability of EBD to successfully alleviate obstruction symptoms in the short term. However, they also introduce an unmet need for a treatment that will be able to improve recurrence rates and further delay the need for surgery.

Various alternatives to standard bare EBD have also been evaluated, with limited success in prolonging patency. Intralesional steroid injection into the stricture site after EBD has been evaluated as a potential method for limiting stricture recurrence; however, it was found that the time to redilation in anastomotic strictures did not differ significantly from standard procedures.²⁵ Intralesional steroid injection may be complicated by inconsistent dosing and sparse delivery of the injected steroid to the stricture using a syringe delivery system. Intralesional injection of long-acting steroids after EBD is not recommended for the treatment of CD stricture by the Global Interventional IBD Group.⁵ The paclitaxel coating on the ProTractX3 DCB is uniformly applied to the balloon body, leading to consistent circumferential delivery and precise dosing of the drug to the treated tissues during dilation of the stricture. Bare metallic stents have also been evaluated as a potential improvement over standard EBD; however, they bring newfound risks such as inflammatory reactions because of a foreign body, stent migration, and perforation in the intestine.¹³ The preclinical assessments conducted here showed that paclitaxel was present during

the key phases of postinjury wound healing but did not lead to increased inflammation, fibrosis, or other negative cellular responses.

The results from the POISE trial introduce a novel approach to limiting fibrosis. Through 2 years of follow-up, no subject required repeat intervention or experienced a recurrence. Furthermore, at 2 years postprocedure, a 97% improvement in their symptom scores from baseline was still evident. The current standard of care only prioritizes alleviating symptoms of obstruction by reducing inflammation. The ProTractX3 DCB treatment not only targets inflammation, but also inhibits proliferation of the cells and matrix with a localized application of paclitaxel. Currently, no other devices on the market address the intestinal bowel stricture healing process in this manner.

The limitations of this study include the small sample size and limited duration of study follow-up. Other limitations may include the lack of a control group and lack of diversity in the population cohort. Malignant strictures were also excluded from this study. However, this is the first report of a paclitaxel-coated balloon used to treat intestinal strictures. The POISE trial was designed as an early phase study to gain initial experience with the device. Pilot studies such as this are typically conducted with a small number of participants to evaluate the early safety and efficacy of the investigational device before evaluating in a larger pivotal trial. Follow-up will continue through the 5-year time point for subjects enrolled in this study. A large randomized controlled trial is planned to evaluate the ProTractX3 DCB against standard EBD and will provide further insight into the risks and benefits associated with this device (clinicaltrials.gov: NCT05561127).

In conclusion, results from preclinical and early human studies conclude that the ProTractX3 DCB shows promising early safety and efficacy for treating intestinal strictures. No systemic or local toxicities were noted during preclinical testing, whereas paclitaxel was confirmed to be present in treated tissues between 7 and 28 days. Participants in the POISE study experienced functional resolution of their stricture and a consistent symptomatic improvement over 2 years with no serious adverse effects. Follow-up will be conducted over 5 years and provide a basis for future large-scale studies to further demonstrate the effectiveness of the ProTractX3 DCB in treating benign intestinal strictures.

DISCLOSURE

All authors disclosed no financial relationships. Research support for this study was provided by GIE Medical.

Abbreviations: CD, Crohn's disease; DCB, drug-coated balloon; EBD, endoscopic balloon dilation; EOS, Endoscope Obstruction Score; IBD, inflammatory bowel disease; OSS, Obstructive Symptom Score.

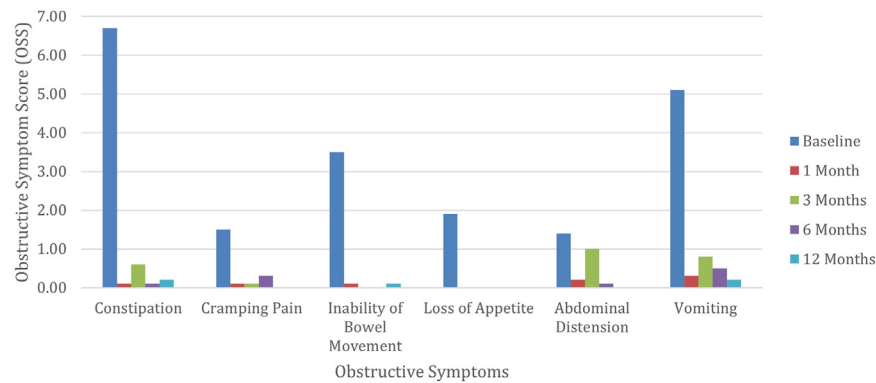


Figure 2. Average scores over time for each symptom component of the Obstructive Symptom Score.

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