Clinical study protocol

Protocol title: "Randomized controlled trial comparing endoscopic balloon dilation versus endoscopic stricturotomy for short strictures (< 3 cm) related to Crohn's disease (the BEST-CD trial)

Primary Investigator."

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Study description

Brief Summary

Crohn's disease (CD) related strictures can be treated endoscopically by endoscopic balloon dilation (EBD) or endoscopic stricturotomy (EST). EBD is is the established endoscopic treatment for short strictures in Crohn's disease. However, roughly half had recurrent symptoms and two third require surgery after EBD. ES have been used initially for endoscopic treatment of patients for whom EBD was unsuccessful. Subsequently it was shown that ES is a better modality for treating CD related strictures (specially short and anastomotic strictures) than EBD lowering the risk of future surgery and procedure related perforation albeit with an increased risk of bleeding. ES was shown to be non-inferior to re-do surgery in chronic pouch anastomotic sinus in ulcerative colitis (UC) and ileocolic anastomotic strictures in CD thus reducing surgical morbidity. However, these two modalities have not been compared in a randomized controlled manner. We aimed to compare the two endoscopic treatments with regard to clinical success, need for surgery or additional endoscopic procedure and safe-

ty in patients with CD who have short (<3 cm), predominantly fibrotic stenosis excluding those in the small bowel not accessible by endoscope/colonoscopy.

Condition or disease	Intervention or treatment
Crohn's disease	**Intervention:** Endoscopic balloon dilation **Intervention**: Endoscopic stricturotomy

Detailed description

Study design: Single centre, open-label, randomized trial to be done in Asian Institute of Gastroenterology, India

Study population: All eligible consecutive patients with CD who developed DE-nova or anastomotic strictures will be included.

Study settings:

The proposed study would be conducted in a high volume tertiary GI centre (Asian Institute of Gastroenterology) performing nearly more than 200 EBD/ES procedures per year with an well established inflammatory bowel disease (IBD) registry with more than 7000 IBD patients under follow up.

The study will be conducted after approval by the institutional ethics committee. Written informed consent would be taken from each participants and the study would conform to the 1975 Declaration of Helsinki ethical guidelines.

Data collection: A survey administration software (google forms) would be used to collect the participant data (age, sex, ethnicity, clinical features, smoking status, details of CD diagnosis, disease phenotype, extra intestinal manifestations, family history, history of intestinal resection, details of stricture diagnosis, details of stricture: degree, number, location, radiological finding: concurrent abscess, fistula, enhancement;

drug history for CD, procedural details: technical success, symptomatic improvement, endoscopic improvement, stricture related emergency visit or hospitalization, complications, subsequent need for additional endoscopic procedures or surgery upto a follow up of 1 year). Follow-up details would be collected via physical visit or telephonic communication.

Technique and instruments: EBD procedures will be performed with wire guided CRE pneumatic balloon (controlled radial expansion balloon, Boston scientific, Marlborough, MA, USA 0of various sizes based on tightness of the stricture (10-12 mm, 12-15 mm, 15-18 mm, 18-20 mm) with graded dilation with inflation pressures varying from 3-8 ATM pressure. Balloon was inflated for at least 2 minutes and slowly deflated. For mild ooze post EBD, balloon tamponade will also done with the same balloon. A maximum of two sessions of dilation will be allowed with a minimum interval of 15-30 days between them. Additional EBD sessions would be considered as additional endoscopic procedure for the purpose of the study.

Endoscopic stricturotomy would be done using a needle knife/insulted tip (IT) knife with the following electrocautery settings : Endocut Q (effect 3, cut duration 1, cut interval 3) as per by global IIBD group consensus.

Definitions: Technical success for EBD was defined as ability to perform the EBD procedure. Scope passage after EBD/stricturotomy was assessed as a separate outcome which was defined as passage of endoscope through the area where EBD/ES was performed. This included colonoscopy for colonic/pouch strictures, endoscope for upper GI and duodenal strictures and an endoscope: motorized spiral or single balloon enteroscopy for small bowel strictures except those in terminal ileum. Clinical

success in EBD/ES was defined as clinical improvement in symptoms (pain/ intestinal, gastric outlet or colonic obstruction symptoms) after the procedure. Sustained clinical success was defined as absence of obstructive symptoms at 1 year follow up. Major adverse events were defined as perforation, bleeding requiring transfusion or any procedure related prolongation of hospitalization period or an endoscopic, radio logic or surgical intervention. Minor adverse events were bleeding not requiring blood transfusion, post procedural pain and any other self limiting complication (e.g., sore throat after spiral enteroscopy) which does not warrant prolongation of hospital stay. Adverse events will be recorded for all the patients; events were considered associated to be with the procedure when a causal association was possible, probable, or definite. Recurrence of symptoms would be defined as re-emergence of symptoms for which the procedure was initially performed.

Sample size

Based on previous retrospective study, symptomatic improvement with EST and EBD (9.5% and 33.5% respectively, the estimated sample size is total 90 (45 in each group) keeping type 1 error as 0.05 and power as 80%.

Randomization

Patients will be randomly assigned (1:1) to receive either EBD (EBD group) or EST (EST group) using a digital en-block randomization system (block size of four).

Data analysis

Statistical analysis: Statistical analysis would be done by using statistical package for social sciences (SPSS, IBM, NY, USA). Chi-square/Fisher's exact test was used to

compare categorical variables and Mann-Whitney test would used to compare continuous variables between the two groups.P-value <0.05 would be considered statistically significant

Timeline: 2 years

Recruitment of 100 CD patients with stenosis requiring EBD or EST over 1 years: follow up over 1 year.

Patient privacy

An organized database for the purpose of this study will be formed based on google form with anonymize data set (i.e. name, address, and full post code will be removed, together with any other information which, in conjunction with other data held by or disclosed to the recipient, could identify the patient) which would be entered by clinical research assistant.

Study design

Study type: Interventional (clinical trial)

Estimated enrolment: 100 patients

Allocation: Randomized

Intervention model: Parallel assignment

Masking: none (open label)

Primary purpose: Therapeutic

Official title: Randomized controlled trial comparing endoscopic balloon dilation versus endoscopic stricturotomy for short strictures (< 3 cm) related to Crohn's disease (the BEST-CD trial)

Estimated start date : August - September 2022 (after ethical approval)

Estimated recruitment completion: July - August 2023

Estimated study completion date: July - August 2023

Arms and interventions:

Arm	Intervention/treatment
Active comparator: Confirmed Crohn's disease with gastro-duodenal or ileo-colonic short (<3 cm) strictures (both de novo and anastomotic) without prior history of endoscopic stricture therapy	**Intervention: Endoscopic balloon dilation** EBD procedures will be performed with wire guided CRE pneumatic balloon (controlled radial expansion balloon, Boston scientific, Marlborough, MA, USA 0of various sizes based on tightness of the stricture (10-12 mm, 12-15 mm, 15-18 mm, 18-20 mm) with graded dilations with inflation pressures varying from 3-8 ATM pressure. Balloon was inflated for at least 2 minutes and slowly deflated. A maximum of two sessions of dilation will be allowed with a minimum interval of 15-30 days between them.

Active comparator Confirmed Crohn's disease with gastro-duodenal or ileo-colonic short (<3 cm) strictures (both de novo and anastomotic) without prior history of endoscopic stricture therapy	**Intervention: Endoscopic stricturotomy with or without stricturoplasty** Endoscopic stricturotomy would be done using either a tri- ple-lumen needle-knife (Boston Scientific, Marlborough, MA) or with a electrosurgical IT knife2 (Olympus Medical Systems, Tokyo, Japan) in the setting of ERCP Endocut on ERBE (USA Incorporated Surgical Systems, Marietta, GA) with the following electrocautery settings: Endocut Q (effect 3, cut duration 1, cut interval 3). Strictures will be incised in a circumferential or radial fashion until an adequate passage of the scope. Endoclips may be applied post stricturotomy to act as keep treated stricture open and to prevent delayed bleeding (referred as stricturoplasty). Choice of endoclips and decision to perform stricturoplasty would be at the discretion of endoscopist.

Outcome measures

Primary outcome measures

To compare sustained clinical improvement post EBD and ES (%) (time frame :

1year): percentage of patients having no obstructive symptoms due to CD related stenosis for which EBD/ES was performed for a period of 1 year

Secondary outcome measures

1. To compare need for additional intervention (EBD/EST/Surgery) between EST and EBD arm (%) : the percentage of patients who require additional interventions for CD related stenosis over period of 1 year
2. To compare technical success between EBD and ES (%): Percentage of patients in whom endoscope is passable after EBD/ES

2. To compare stricture related visit to the emergency department after EST versus EBD: percentage of patients visiting the emergency department for CD stenosis related symptoms post EBD/ES over period of 1 year

3. To compare structure related hospitalization with EST versus EBD: percentage of patients visiting undergoing hospitalization for CD stenosis related symptoms post EBD/ES over period of 1 year

4. To compare complications related to EST versus EBD: Major adverse events will be defined as perforation, bleeding requiring transfusion or any procedure related prolongation of hospitalization period or an endoscopic, radio logic or surgical intervention. Minor adverse events were bleeding not requiring blood transfusion, post procedural pain and any other self limiting complication which does not warrant prolongation of hospital stay. Adverse events were considered associated to be with the procedure when a causal association was possible, probable, or definite.

Eligibility criteria

Ages eligible for the study : 18 Years to 65 Years (Adult, Older Adult)

Sexes eligible for the study: all

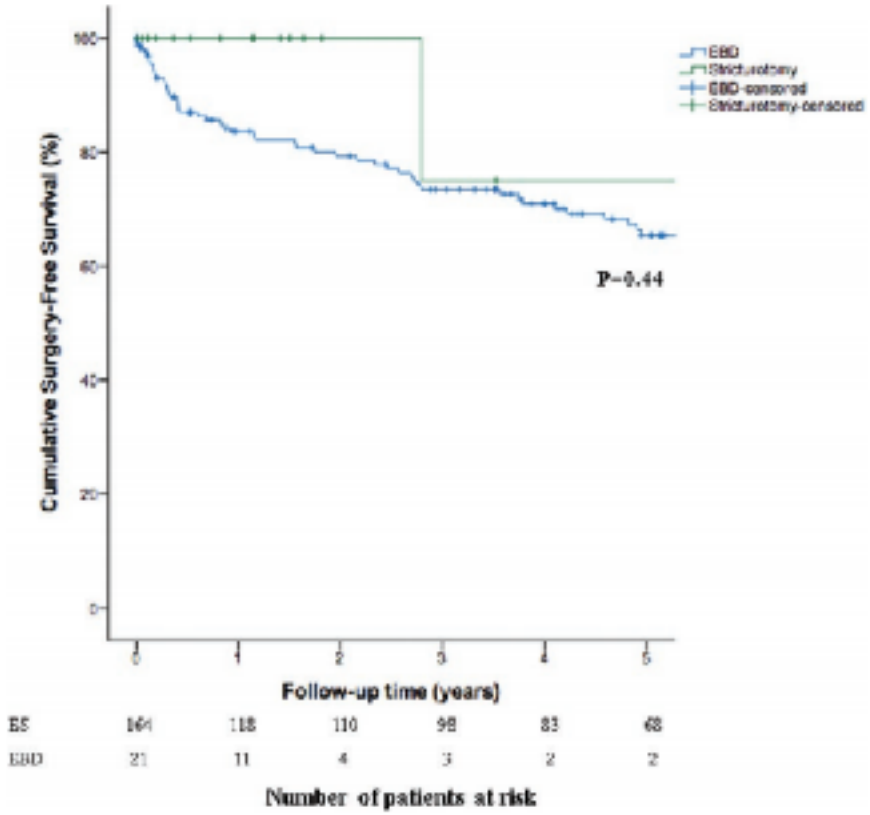
Accepts healthy volunteer: no

Authors	Patients (N)	Location	Technical Success	Adverse events
Lan et al 2015	85	Multiple locations	100%	3.7%
Lan et al 2018	21	Anastomotic	100%	8.8%
Lan et al 2019	35	Anastomotic	100%	10.2%
Zhang et al 2019	49	Multiple locations	100%	4.7%
Lan et al 2019	40	Pouch Inlet	100%	4.7%
Kochhar G 2020	11	Multiple locations	92%	9.0%
Lan et al 2020	13	Terminal Ileum	100%	6.9%
Moroi et al 2020	5	Anastomotic	100%	20%

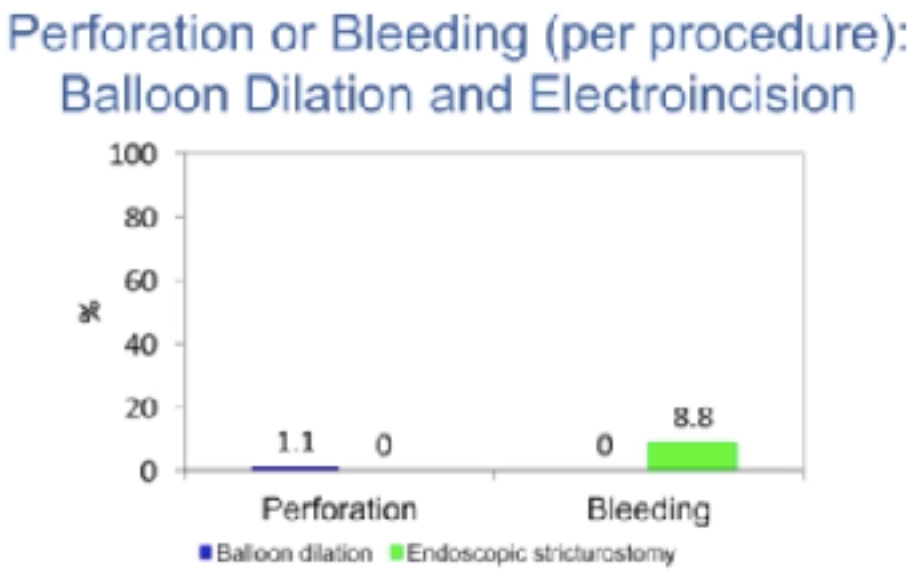
Criteria

Outcome	Stricturotomy (n=21)	Balloon Dilation (n=164)	*P* value
Follow-up time, year	0.8 (0.1–1.6)	4.0 (0.8–6.9)	<0.001
Age at procedure, year	43.3 ± 14.5	42.8 ± 13.4	0.76
Duration from last surgery to procedure, year	6.4 (1.7–16.4)	7.8 (3.6–13.3)	0.56
Duration from CD diagnosis to procedure, year	19.6 (11.4–8.1)	16.6 (9.9–25.8)	0.85
Immediate technical success	21 (100.0%)	147 (89.5%)	0.25
Symptomatic improvement	8/11 (72.7%)	59/103(45.4%)	0.08
Endoscopic improvement	8/17 (47.1%)	57/163(35.0%)	0.32
Escalation of drug after procedure	13 (61.9%)	53 (32.3%)	0.09
Additional endoscopic therapy (EBD or ES)	6 (28.6%)	98 (59.8%)	0.85

Outcome		Stricturotomy (N=21)	Balloon Dilation (n=164)	*P* value
Disease related emergency department visits		2 (9.5%)	40 (24.4%)	0.74
Stricture-related	Per Patients	1 (2.0)	34 (20.7%)	0.33
	Per visit	4/11 (36.4%)	78/104(75.0%)	0.001
Disease related hospitalization		7 (33.3%)	40 (24.4%)	0.93
Stricture related	Per Patients	1 (4.8%)	33 (20.1%)	0.16
	Per visit	2/12 (16.7%)	57/102(55.9%)	0.35
Complication				
Perforation	Per patients	0/21 (0.0%)	4/164 (2.4%)	1.0
	Per procedures	0/45 (0.0%)	5/478 (1.1%)	
Transfusion required bleeding	Per patients	3/21 (14.3%)	0/164 (0.0%)	<0.001
	Per procedures	4/45 (8.8%)	0/478 (0.0%)	
Subsequent surgery		2 (9.5%)	55 (33.5%)	0.03



5-year surgery-free survival curve after treated with endoscopic stricturotomy (ES) versus endoscopic balloon dilation (EBD).



Inclusion Criteria:

Primary confirmed diagnosis of CD with obstructive symptoms

1) Gastro-duodenal and ileo-colonic strictures (both de novo and anastomotic strictures)

2) Short strictures (<3 cm)

3) Fibrotic or mixed stricture (predominantly fibrotic)

4) Strictures treated with either EST or EBD.

Exclusion Criteria:

1. No established diagnosis of CD;
2. No endoscopic therapy; and
3. A combination therapy of EST and EBD at the onset
4. Small bowel CD related stricture requiring enteroscopy guided dilation
5. Predominantly ulcerated strictures (mixed or pure ulcerated strictures)
6. Long strictures (>3 cm)
7. Pediatric Patients (<18 years)
8. Pregnant or lactating mother
7. Not willing to participate

Studies on ESTST vs EBD CD related anastomotic strictures

Experience of the key project personnel

Dr. PARTHA PAL, MD, DNB, MRCP (UK)) : Consultant Gastroenterologist with special interest in IBD research at IBD Center, Asian Institute of Gastroenterology,

Hyderabad India. He runs the IBD Clinic at the AIG, Somajiguda unit with an established IBD registry and is actively involved in research in the field of IBD with numerous publications. He is also a co-investigator of numerous clinical trials in IBD.

Declaration of Investigator

I have read and understood all sections of the protocol entitled "Randomized controlled trial comparing endoscopic **b**alloon dilation versus **e**ndoscopic **st**ricturotomy for short strictures (< 3 cm) related to **C**rohn's **d**isease (**the BEST-CD** trial)" in the accompanying investigator's brochure. I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version including country specific dated the International Council for Harmonization harmonized tripartite guideline E6(R2): Good Clinical Practice and the Declaration of Helsinki (WMA2013), and all applicable government regulations. I will not make changes to the protocol before consulting implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to perform the procedure only to patients under my personal supervision or the supervision of a sub-investigator. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

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Signature of Principal Investigator Date

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Printed Name of Principal Investigator