

Open label, prospective, randomized controlled trial of an endoscopic duodenal-jejunal bypass sleeve versus low calorie diet for pre-operative weight loss in bariatric surgery

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Abstract

Background The duodenal-jejunal bypass sleeve (DJBS) has been shown to achieve a completely endoscopic duodenal exclusion without the need for stapling. This report is the first randomized controlled trial for weight loss.

Methods In a 12-week, prospective, randomized study, subjects received either a low fat diet and the DJBS or a low fat diet control (no device). Twenty-five patients were implanted with the device and 14 received the control. The groups were demographically similar. Both groups received counseling at baseline only, which consisted of a low calorie diet, and exercise/behavior modification advice. No additional counseling occurred in either group. Measurements included starting and monthly body weight and serum blood tests. The device group also had a plain abdominal film post implant, a monthly KUB and a 4-week post explant EGD.

Results Twenty device (80%) subjects maintained the DJBS without a significant adverse event for the 12-week duration. At 12 weeks, the mean excess weight loss was

22% and 5% for the device and control groups, respectively ($p < 0.001$). Five subjects (20%) were endoscopically explanted early secondary to upper GI (UGI) bleeding ($n = 3$), anchor migration ($n = 1$) and sleeve obstruction ($n = 1$). The UGI bleeding occurred at a mean of 13.8 days post implant. EGD was performed in each of these cases with no distinct bleeding source identified. No blood transfusion was required. The migration occurred on day 47 and manifested as abdominal pain. The subject with the sleeve obstruction presented with abdominal pain and vomiting on day 30. Eight subjects (40%) underwent the 4 week post explant EGD at which time mild degrees of residual duodenal inflammation was noted.

Conclusion The DJBS achieves noninvasive duodenal exclusion and short term weight loss efficacy. Longer term randomized controlled sham trials for weight loss and treatment of T2DM are underway.

Keywords Obesity · Endoscopy · Duodenal bypass · Preoperative weight loss

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The concept of body weight regulation before elective surgery has long been recognized. Studies show that excess weight and all spectrums of obesity complicate the short- and long-term outcomes of surgical interventions in a variety of ways [1–9]. It is reported that even a modest 10% reduction of excess body weight before elective surgery significantly reduces obesity-related risks associated with anesthesia, pulmonary dysfunction, diabetes and hypertension, and other comorbid physiologic conditions [10]. These concepts have been so well established that overweight, obesity, and morbid obesity are now relative contraindications to such procedures as hernia repair, joint replacement, and organ transplantation [1–5].

The use of preoperative weight loss in these fields is becoming more common given the evidence concerning the impact of overweight and obesity on the outcomes of the aforementioned procedures. In addition to optimizing the overall health of patients preparing for bariatric surgery in particular, preoperative weight loss also can function to test patients' motivation toward weight loss, to accustom patients to a lifestyle of restrictive food intake, and to augment postoperative weight loss [6–9].

Despite increasing adoption of preoperative weight loss in preparation for bariatric surgery, a minority of patients are capable of achieving the goal of weight loss on their own [9]. The duodenal-jejunal bypass sleeve (DJBS, now the EndoBarrier; GI Dynamics, Inc., Lexington, MA, USA) is a 60-cm-long fluoropolymer liner anchored endoscopically in the duodenum to create a duodenal-jejunal bypass (Fig. 1).

A combination of fluoroscopy and endoscopy is used to deliver the device. The implant is delivered via an over-the-wire catheter system, then contained within a capsule at the distal end of the catheter. Once the capsule is placed in the duodenum, an inner catheter is pushed and the bowel negotiated with the aid of an atraumatic ball attached to the distal end of the catheter. The sleeve is attached to the catheter, which pulls the sleeve out of the capsule.

After the sleeve is fully deployed, the anchor is deployed from the capsule to sit within the duodenal bulb. The anchor self-expands, and the barbs engage the tissue to prevent movement. Contrast is flushed to ensure patency of the sleeve. The sleeve and ball are detached from the catheter, and the catheter is removed from the bowel, leaving the implant in place.

The first human experience with the DJBS as a weight loss adjunct before gastric bypass was recently published [11]. That pilot report describes the DJBS implanted in 12 subjects awaiting gastric bypass. Over the course of this

12-week trial, the subjects experienced an average excess body weight loss (EWL) of 23.6%, with all the patients achieving at least 10% EWL. The purpose of the current trial was to evaluate more rigorously the safety and efficacy of the DJBS for weight loss before bariatric surgery.

Methods

This open-label, multicenter, prospective, randomized controlled trial compared the use of the EndoBarrier with a low-calorie diet alone for weight loss before bariatric surgery. The trial, initially designed for 12 weeks, was extended to 24 and then to 36 weeks. The focus of this report is on the initial 12 weeks only because follow-up data for the extended period is incomplete at this writing.

This trial, conducted according to the principles of good clinical practice and in compliance with the Medical Device Regulations for Chile, included ethics committee approval and subject consent. The inclusion and exclusion criteria, shown in Table 1, largely reflect current guidelines on patient selection for bariatric surgery.

The primary 12-week efficacy end point was assessment of the difference in %EWL between the device and control groups. There were two 12-week secondary end points: (1) improvement in type 2 diabetic status, defined as a 0.5% reduction in HbA_{1c} from baseline and/or reduction, or elimination of diabetic medications; and (2) the percentage of subjects who achieved at least a 10% EWL. Safety was assessed as the incidence and severity of adverse events (device and non-device related). Safety and efficacy were assessed by the use of descriptive statistics and a complete review of data listings.

All the device subjects were seen for a baseline examination that included a history, physical examination, baseline demographics, electrocardiogram, chest radiograph, abdominal ultrasound, surveillance upper endoscopy, and fasting blood tests. After implantation of the device, plain abdominal radiography of the kidneys, ureters, and bladder (KUB); completion of a satiety questionnaire; and safety assessments were performed at monthly intervals. The control subjects also were seen for a history, physical examination, collection of baseline demographics, and fasting blood tests. The subjects were randomized by a computer-generated code.

Weight loss counseling on diet, exercise, and lifestyle modification advice was provided for the subjects in both groups only at the baseline visit. Except for the upper endoscopy required for screening and implantation/removal of the device and the KUB surveillance, all the subjects were followed and treated equally throughout the trial. This included weigh-in and safety examinations at weeks 1, 4, 8, and 12.



Fig. 1 The duodenal-jejunal bypass sleeve

Table 1 Inclusion and exclusion criteria

Inclusion criteria

- Age 18–55 years (male or female)
- BMI ≥ 35 with significant comorbidities (i.e., hypertension, hyperlipidemia, or diabetes) or BMI 40–60 (with or without a comorbid condition)
- History of failure with nonsurgical weight loss methods
- Candidates for Roux-en-Y gastric bypass
- Subjects willing to comply with study requirements
- Subjects who signed an informed consent form

Exclusion criteria

- Subjects requiring prescription anticoagulation therapy
- Subjects with iron deficiency and iron deficiency anemia
- Subjects with inflammatory bowel disease or conditions of the gastrointestinal tract, such as ulcers or Crohn's disease
- Subjects for whom treatment would have presented an unreasonable risk
- Subjects with pancreatitis or other serious organic conditions
- Subjects with symptomatic coronary artery disease or pulmonary dysfunction
- Subjects with gallstones before implantation
- Subjects with infections at the time of implantation
- Subjects with severe coagulopathy, upper gastrointestinal bleeding conditions such as esophageal or gastric varices, or congenital or acquired intestinal telangiectasia
- Subjects with congenital or acquired anomalies of the GI tract such as atresias or stenoses
- Subjects who were pregnant or had intentions of becoming pregnant during the study duration
- Subjects with unresolved alcohol or drug addiction
- HIV-positive subjects
- Subjects with hepatitis B or C
- Subjects who were mentally retarded or emotionally unstable, or exhibited psychological characteristics that in the opinion of the investigator made the subject a poor candidate for device placement or clinical trial
- Subjects who had previous GI surgery that would potentially affect the ability to place the sleeve or the function of the implant.
- Subjects unable to discontinue nonsteroidal antiinflammatory drugs (NSAIDs) during the implantation period
- Subjects who were *Helicobacter pylori* positive (Note: Subjects could be enrolled if they had a history of *H. pylori* and were successfully treated.)
- Subjects taking weight loss medications such as Meridia and Xenical
- Subjects who had a family with or a history of a known diagnosis or preexisting symptoms of systemic lupus erythematosus, scleroderma, or other autoimmune connective tissue disorder
- Subjects who had gastroesophageal reflux disease (GERD)
- Subjects with a history of kidney stones
- Subjects participating in another ongoing investigational clinical trial

GI, gastrointestinal; HIV, human immunodeficiency virus

All the subjects were instructed to stay on a liquid diet for the first postimplantation week, followed by a pureed diet for the second week. At the 2-week follow-up visit, all the subjects were advanced to a regular diet. The complete follow-up schedule is shown in Table 2.

Results

Demographics

Of the 44 subjects screened, 40 met the study criteria and were randomized to receive either the DJBS or the diet

control. A total of 26 subjects were randomized to the device, and 25 were successfully implanted. One subject could not be implanted with the device because of duodenal anatomy. This subject was excluded from the analysis. A total of 14 subjects were randomized to the control group. The last 15 consecutive patients to enroll were assigned to the device arm of the study for the purpose of increasing the number of subjects with the DJBS in this pilot trial.

The device group consisted of 10 men and 15 women, and the control population comprised 6 men and 8 women. The average age was 38 ± 10.1 years (range, 23–56 years) for the device subjects and 43 ± 10.6 years (range, 25–

Table 2 Evaluation schedule

	Baseline (14 days before implantation)	Postimplant (within 24 h before implantation)	Weeks 1, 4, 8 (± 3 days)	Week 12 (± 3 days)	72 h and 4 weeks after explantation (± 3 days) (device subjects only)
History and physical exam	X			X (physical exam only)	
ECG and CXR	X (device-only group)				
Weight/BMI/waist circumference	X		X	X	
Liver, biliary duct, & pancreas ultrasound	X (device only group)				
Upper endoscopy (only once for procedure)				X (at explantation for device group only)	X (at explantation for device group only)
Fasting bloods: Total bilirubin Gamma GT SGOT SGPT LDH ALK phosphatase Total cholesterol HDL LDL Triglycerides Glucose Amylase Lipase HbA _{1c} Insulin level.	X		X	X	
Adverse event Assessment	X	X	X	X	X
Abdominal X-ray		X (device group only)	X (device group only)	X (device group only)	
Nutritional counseling	X				

ECG, electrocardiogram; CXR, chest X-ray; BMI, body mass index; GT; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; LDH, lactic dehydrogenase; ALK, alkaline; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA_{1c}

57 years) for the control subjects. The average body mass index (BMI) was 42 ± 5.1 (range 35–54) for the device group and 40 ± 3.5 (range, 36–47) for the control group. The mean starting weight was 114 ± 20.9 kg (range, 81–172 kg) for the device group and 108 ± 12.0 kg (range, 86–122 kg) for the control group. Four subjects had type 2 diabetes: three in the device group and one in the control group.

Follow-up care

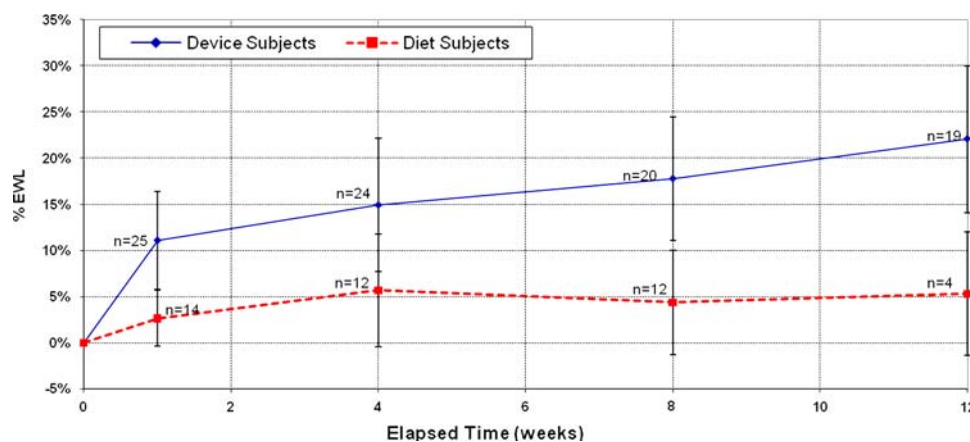
The 12-week protocol was completed by 20 device subjects and 4 control subjects, with 10 control subjects lost to follow-up evaluation at 12 weeks. Five devices were

removed before 12 weeks because of intraluminal hemorrhage at a mean of 13.8 ± 2.9 days (range, 12–17 day) ($n = 3$), sleeve obstruction at 30 days ($n = 1$), and a 2-cm anchor migration at 47 days ($n = 1$).

Weight loss

At 12 weeks, the average %EWL was $22.1\% \pm 8\%$ for the device group and $5.3\% \pm 6.6\%$ for the control group ($p = 0.02$) (Fig. 2). This corresponds to an average absolute weight reduction of 10.3 ± 3.2 kg (range, 4.5–18 kg) for the device subjects and 2.6 ± 3.5 kg (range 0–7.7 kg) for the diet subjects. By the end of their trial participation, 23 (92%) of the 25 device subjects and 3 (21%) of the 14

Fig. 2 Percentage of excess weight loss using the device compared with that using diet alone



diet control subjects had achieved at least a 10% EWL ($p = 0.0001$). The five explanted patients were not included in this analysis because they went on to have gastric bypass surgery within weeks of the explantation.

Satiety

At 12 weeks, 17 of 19 device subjects reported greater satiety than before implantation with the DJBS. One device subject reported less satiety than before the implantation, and one reported the same satiety. All four control subjects reported less satiety 12 weeks after implantation than at baseline.

Type 2 diabetes

Four subjects had type 2 diabetes. Three were treated with the device, and one was treated under the control arm of the study. All four diabetics improved by week 1 and maintained this status throughout the duration of the trial. The diabetic status of one device subject improved further and was reported as resolved at week 12. "Improvement" was defined as reduced oral hypoglycemic/insulin medications and "resolved" was defined as off medications with normal fasting plasma glucose and normal glycosylated hemoglobin. The baseline and final fasting plasma glucose, HbA1c data, and %EWL for each of these subjects are shown in Table 3. The average %EWL was $19\% \pm 13.6\%$ at 12 weeks.

Implant procedure safety

The device subjects received a proton pump inhibitor the evening before their device implantation and were advised to continue receiving this medication throughout the protocol. All procedures were performed with the patient under general anesthesia. The average implantation time was 38.9 ± 27 min (range, 14–111 min), with an average fluoroscopy time of 13.3 ± 6.7 min (range, 2–27 min) of. Five subjects required multiple implantation attempts in the same setting because of difficulty advancing the catheter or positioning the anchor in the duodenal bulb. There was one procedure-related adverse event described as noncardiac chest pain.

Explantation procedure safety

All 25 device subjects were successfully explanted endoscopically. The mean explantation time was 21 ± 17 min (range, 3–70 min), with a mean fluoroscopy time of 4.1 ± 4.2 min (range, 1–18 min).

Device in situ safety

No signs or symptoms of biliary or pancreatic duct obstruction were observed throughout the trial. No clinically significant abnormal blood values were reported except for an acute drop in hemoglobin and hematocrit in the subjects with intraluminal hemorrhage. A total of 16 subjects, all in the device group, reported at least one adverse event. Of the 56 adverse events reported, 48 (86%) were possibly or definitely related to the device, including abdominal pain ($n = 16$), nausea ($n = 7$), vomiting ($n = 8$), abdominal distension ($n = 11$), gastrointestinal hemorrhage ($n = 4$), constipation ($n = 1$), and epigastric discomfort ($n = 1$). All these events except five were considered mild or moderate by the investigators. The five severe events included gastrointestinal hemorrhage ($n = 3$), abdominal pain ($n = 1$), and vomiting ($n = 1$).

Discussion

This trial aimed to continue evaluating the safety and effectiveness of a new endoscopic device for the treatment of obesity. Bariatric surgeons have increasingly mandated that weight loss surgery patients lose at least 10% of their excess body weight before surgery. This is done to reduce physiologic stress and enhance the technical ease with which these procedures can be performed [6–10]. Still et al. [9] showed that an excess weight loss of 5% to 10% before gastric bypass led to shorter hospital stays and more rapid postoperative weight loss. Of particular significance in this series, which included intensive weight loss counseling, only 48% of the population achieved more than a 10% excess weight loss. This is in stark contrast to the results achieved during both EndoBarrier clinical trials, in which more than 94% of the device subjects were able to achieve this outcome [11].

Table 3 Type 2 diabetes outcomes

Subject	Baseline HbA1c (%)	Week 12 HbA1c (%)	Medication status	%EWL (%)
101 (diet)	12.6	7.8	Discontinued at week 1	+0.8
122 (device)	5.5	5.8 (week 8)	Discontinued at week 1	31.6
202 (device)	7.8	7.1	Decreased at week 9	20.3
219 (device)	6.6	6.0	Decreased at week 8	22.9

%EWL, percentage of excess weight loss

In the only prospective randomized trial investigating preoperative weight loss, Alami [7] evaluated the impact of preoperative weight loss in bariatric surgery. In this trial, 100 demographically similar gastric bypass candidates were randomly assigned either to lose 10% of their body weight or to go on to surgery at their presenting weight. The variables analyzed included incidence of surgical complications, operating time, postoperative weight loss, and resolution of comorbid conditions. Data were available for 26 weight loss and 35 non-weight loss candidates. The authors reported that patients who achieved a 10% excess weight loss preoperatively had a shorter operating time (220.2 vs 257.5 min; $p = 0.0084$) and enhanced postoperative weight loss at 3 months (44.1% vs 33.1%) compared with the non-weight loss group ($p = 0.0267$). In this small series, the incidence of surgical complications and the resolution of comorbid health conditions did not differ between the two groups.

Alvarado et al. [6] studied 90 patients with respect to preoperative weight loss and its impact on postoperative weight loss and resolution of comorbidities. The mean starting BMI was 48.1, and the mean %EWL at the start was 7.25%. The postoperative weight loss at 12 months was 74.4%. A preoperative initial weight loss of 1% correlated with a 1.8% increase in postoperative excess weight loss at 1 year. In addition, initial BMI correlated negatively with EWL: an increase of 1 BMI unit was related to a 1.34% decrease in excess weight loss. Finally, a preoperative weight loss greater than 5% correlated significantly with shorter operative times by 36 min. In this small trial, preoperative weight loss did not correlate with postoperative complications or correction of comorbidities likely due to the small sample size.

In another retrospective review, Liu et al. [8] compared 48 patients who lost, on the average, 4.8% of their excess weight before bariatric surgery with a cohort of 47 patients who gained an average of 4.8% before surgery. There were no differences between the two groups in age, gender, American Society of Anesthesiology (ASA) class, comorbidities, or BMI at surgery. The preoperative weight loss group had less intraoperative blood loss (102 vs 72 ml; $p = 0.03$), and the surgeon also was less likely to report an enlarged liver ($p = 0.02$) compared with the weight gain cohort. Additionally, the operation was less likely to deviate from the standard laparoscopic gastric bypass in the preoperative weight loss group ($p = 0.02$). No differences were seen in operative time, length of hospital stay, wound infections, or major complications.

This trial demonstrated that the EndoBarrier can be safely implanted via a completely endoscopic technique, maintained in situ in a majority of subjects for a 12-week period, and explanted via an endoscopic approach. The device was extremely well tolerated by the majority of the

subjects. Although reports of abdominal pain were frequent in the first 2 weeks, such symptoms uniformly abated and were the suspected result of anchor expansion in the early time frame. Reports of abdominal pain after the first 2 weeks were nearly always related to bouts of dietary indiscretion, perhaps indicating gastric emptying effects of the device that could be functional, neurohumoral, or mechanical in nature. These symptoms may be a desirable side effect of the device helping to provide feedback for reducing caloric intake.

The satiety assessments showed that 90% of the device subjects reported early and prolonged satiety compared with their preimplant status. This could prove an important mechanism by which the EndoBarrier leads to body weight reduction.

The statistically significant difference between weight losses in the device and control arms of the study represents an exciting preliminary look at the potential efficacy of the EndoBarrier. The fact that at 12 weeks the average %EWL was 22.1% for the device subjects and 5.3% for the control subjects highlights the efficacy of the EndoBarrier in helping subjects lose weight in the short term. In addition, the fact that 92% of the device patients were able to achieve at least a 10% EWL highlights the acceptance of this approach compared with current dieting alternatives, which achieved a similar result for only 21% of the control subjects.

The improvement and resolution of type 2 diabetes seen in this trial also represents a preliminary look at the potential impact of this technology. It has been widely postulated that duodenal bypass alone may be the most important mechanism by which gastric bypass achieves rapid resolution of type 2 diabetes [12]. The EndoBarrier represents a novel mechanism by which this diversion can be achieved without the need for stapling or reanastomosis. These preliminary data have led to an ongoing clinical trial specifically aimed at investigating the role of the EndoBarrier in the treatment of type 2 diabetes.

One implantation procedure-related adverse event occurred. In this case, the endoscope and the capsule portion of the delivery catheter were inadvertently placed side by side in the esophagus. This resulted in a temporary distention of the esophagus, which manifested clinically as chest pain. This event was rated mild by the investigator. The subject underwent electrocardiogram and cardiac enzyme analysis, and the results for both were negative. The pain was ultimately self-limited and of no long-term significance.

Although we remain encouraged with the efficacy of the EndoBarrier compared with a low-calorie diet control, several technical limitations and learning curve issues have been identified through this investigation. Five subjects required more than one implantation attempt in

the same setting given aberrant placement of the device initially. We believe that this relates entirely to procedural development and the early learning curve. Only one of these subjects underwent an early explantation on day 30 due to a sleeve obstruction that caused abdominal pain and vomiting. Given the difficult delivery in this case, we believe the sleeve may have been twisted incidentally during implantation and was not fully patent from the start. Subsequently, physicians participating in this trial were retrained to check the patency of the device by flushing it with saline plus contrast before completing the implantation procedure.

Despite the highly favorable in situ safety profile, several early explantations occurred in the initial 12-week time frame. In three cases of intraluminal hemorrhage, meticulous upper endoscopic examination was performed after device removal, and none of these cases showed a defined bleeding source. Each of these episodes was self-limited, with no need for further endoscopic intervention or blood transfusion.

We believe that the anchor and its interaction with the duodenal wall likely played a role in the bleeding. Although some degree of bleeding may be expected given the interaction of the anchor with the duodenum, we speculate that a device modification of the barb design may have contributed to the bleeding seen in this trial. No bleeding occurred in the previously published safety trial [11]. The original design provided a rounded barb dull to the touch. A careful review of the barbs used in this trial versus those used in the first trial showed that the barbs produced for this trial were considerably sharper. We postulate that the dull barbs penetrate the tissue slowly and create a snowplowing effect whereby vessels are pushed aside. The sharper barbs may penetrate the tissue immediately and more easily tear tissue and vessels. As a result of this analysis, the dull barb design has been reinstated and currently is under investigation in ongoing clinical trials.

The final early device removal involved a device that had migrated 2 cm from its original position. The subject presented with abdominal pain and several episodes of hematemesis. This episode took place 47 days after implantation, and the device was subsequently removed. We believe the hematemesis was attributable to the migration, at which point the barbs may have cut tissue as the anchor moved down the duodenum. A thorough endoscopic examination immediately after device removal showed no trauma at the original anchor site and no active bleeding. Furthermore, follow-up endoscopic examination failed to demonstrate an active bleeding point. The subject required a 4-unit blood transfusion and recovered with no further complications.

Conclusion

Preoperative weight loss is becoming an increasingly important component in the care of the weight loss surgery patient. The safety and efficacy of the EndoBarrier demonstrated in this trial and the previous safety trial illustrate an important potential role for this technology in the ongoing quest for completely endoscopic weight loss solutions. Improvements to the stability and safety of the EndoBarrier remain the subject of ongoing research and development efforts. Additional clinical trials investigating the role of the EndoBarrier in the treatment of obesity and type 2 diabetes are warranted and currently ongoing.

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