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Endoscopic full-thickness plication: the device, technique, pre-clinical and early clinical experience

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Heartburn and regurgitation, the most common symptoms associated with gastroesophageal reflux disease (GERD), are present daily in approximately 7% of adults in the United States. GERD is associated with serious complications, such as esophageal strictures, Barrett's metaplasia and adenocarcinoma of the esophagus [1]. GERD sufferers have a lower quality of life than patients with other chronic illnesses such as angina and heart failure [2].

Antisecretory medications are the most common and effective pharmacological treatment for GERD. [3–5]. Anti-secretory medication does not prevent the reflux of gastric contents into the esophagus, therefore, whereas they often relieve heartburn, other symptoms such as regurgitation, often persist. Because GERD is a chronic disease, many patients require chronic therapy.

Surgical therapy has become increasingly common for the treatment of GERD. The most commonly performed antireflux surgery is the Nissen fundoplication [6]. A study comparing open Nissen fundoplication to omeprazole 20 mg/day has found surgery superior to omeprazole for the treatment of erosive esophagitis after 5 years of follow up [7]. If the dose of omeprazole, however, was increased during periods of relapse, the two therapeutic strategies had a similar efficacy. The long-term durability of surgery is not known, however, one study reported 63% of patients who underwent a Nissen fundoplication to be using anti-secretory medications at a mean follow-up of 10.6 years [8]. Nissen fundoplication has been associated with significant morbidity, including gas, bloating and dysphagia in up to 5% of patients [9]. Potential advantages of an endoscopic procedure over a surgical antireflux procedure include lower costs, shorter post-operative recovery time and discomfort, and potentially fewer

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complications. An endoscopic reflux procedure could also be an attractive alternative to long-term acid suppression.

The Endoscopic Full-Thickness Plication System (NDO Surgical, Inc, Mansfield, MA) is designed to inhibit reflux with a single plication near the gastroesophageal junction. This is possibly caused by the ability of the device to consistently perform a transmural plication rather than a submucosal or intramuscular plication. The serosa-to-serosa tissue union that is created seems to accentuate and restore the valvular mechanism of the gastroesophageal junction.

Device and technique

Endoscopic full-thickness plication system

The full-thickness Endoscopic Plication System (NDO Surgical, Inc., Mansfield, MA) is designed to fixate stomach tissue near the gastroesophageal junction with serosa-to-serosa apposition. The first generation system consists of a reusable instrument and a single-use suture-based implant. Additionally, a proprietary endoscopic tissue retractor and standard overtube are used to perform the endoscopic full-thickness plication procedure. A schema of the endoscopic plication system is shown (Fig. 1).

Instrument

The Endoscopic Plication System reusable instrument passes two needles through tissue at the desired location to place the implant for tissue approximation, plication and fixation. Controls on the instrument handle actuate the distal end of the device, providing for retroflexing the distal end, opening and closing the instrument arms, and deploying the implant. The Plicator instrument

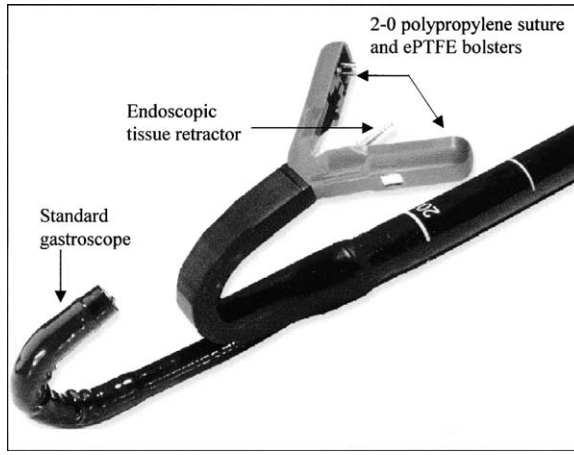

Fig. 1. Schema of endoscopic full-thickness plication system.

contains two working channels, one for insertion of the tissue retractor, the other for passage of the gastroscope.

Endoscopic tissue retractor

The endoscopic tissue retractor is designed to engage the gastric wall up to the level of the serosa, allowing for creation of the full-thickness plication. The tissue retractor is made of stainless steel and biocompatible polymers and includes a protective outer sheath to stabilize the mucosa while engaging the gastric wall and provide a depth stop for retractor insertion. Once inserted, the tissue is pulled into the open arms of the instrument so that the implant can be safely deployed.

Implant

The implant, which allows for fixation of the transmural plication, consists of pre-tied suture, two bolsters, and two titanium retention bridges. The suture is standard USP Size 2-0 polypropylene and is pre-tied and pre-threaded onto the retention bridges. The suture bolsters are made of soft, flexible expanded polytetrafluoroethylene (ePTFE). All implant materials are biocompatible and maintained following the procedure.

Endoscopic plication procedure

The first generation instrument must be passed through an overtube. After endoscopic inspection of the stomach is performed, a Savary wire is passed through the gastroscope. The gastroscope is removed and a Savary dilator and specially designed overtube are passed over the guidewire. The dilator and guidewire are removed, and the Plicator and gastroscope assembly are passed into the stomach. The overtube is retracted so that its distal end is proximal to the gastroesophageal junction and the stomach is distended with air. The gastroscope is advanced and retroflexed so that the instrument may be visualized, retroflexed, and properly positioned. The endoscopic tissue retractor is then inserted within 1 cm of the gastroesophageal junction and advanced up to the level of the serosa. As the serosa is reached, a noticeable tenting up of tissue occurs around the entry point of the retractor, which serves as a visual cue signaling the serosa has been reached. The full-thickness of the gastric wall is retracted and the instrument arms are closed. The implant is then deployed to secure the full-thickness plication, and the tissue retractor is disengaged from the gastric wall. The arms are opened, and the instrument is disengaged from the implant. After closing the arms and straightening the instrument and the gastroscope, both are removed followed by the overtube. A schema of the endoscopic plication procedure is shown (Fig. 2). The second generation plicator passes directly over a Savary wire, eliminating the need for an overtube.

Safety study in pigs

Animal testing was conducted to establish the safety of the endoscopic plication procedure and the implant, and to investigate the implant's ability to

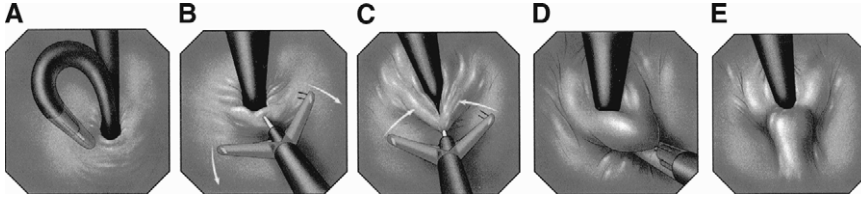

Fig. 2. Endoscopic full-thickness plication technique: (A) plicator and gastroscope retroflexed toward GE junction; (B) tissue retractor advanced to level of serosa; (C) gastric wall retracted, arms closed; (D) single, pre-tied implant is deployed, securing serosa-to-serosa plication; (E) full-thickness plication.

maintain extraluminal tissue apposition long enough for adhesion of tissue layers to occur [10].

All procedures were performed endoscopically, with concurrent laparoscopy performed in one swine studied. The plications were performed at different locations near the gastroesophageal junction. Following plication, behavior was monitored and repeat endoscopy was performed before euthanizing the mini-swine at 0 (n = 1), 3 (n = 4), 6 (n = 2), and 12 (n = 4) weeks.

Sixteen full-thickness plications were created in 11 mini-swine within 1 cm of the gastroesophageal junction at different locations. No complications or deaths occurred in any of the animals studied. Eating habits, posture, respiratory rate, and vocalization of all mini-swine were deemed normal before sacrifice. No signs of tissue damage or trauma were noted on endoscopic observation or on inspection of excised tissue at each study point (ie, 0, 3, 6, and 12 weeks). In one swine, laparoscopy was performed simultaneously with endoscopic full-thickness plication to further verify the safety of the endoscopic technique. Laparoscopy confirmed the serosa-to-serosa tissue apposition with no engagement of surrounding viscera. Even though the follow-up period for this study was 12 weeks, the serosa-to-serosa union seen after only three weeks suggests the durability of the procedure.

Efficacy in porcine model

Procedures were performed on excised pig stomachs to investigate the effectiveness of the plication procedure in reducing reflux, and to compare the effect of placing the plication in different locations around the gastroesophageal junction [10].

Twenty excised pig stomachs were prepared by making an incision in the inferior aspect of the greater curvature. Intragastric contents were removed and the incision was closed. A polyvinyl chloride (PVC) inflow tube was inserted into the duodenum and sealed in place with a clamp. A 16-gauge needle was inserted into the gastric lumen through the anterior wall of the stomach and connected with a PVC tube to a pressure gauge (Fig. 3).

To perform the plications, a hand-held rigid version of the plication system was used (Figs. 4,5). A full-thickness plication was placed in one of the four stomach quadrants within 1 cm of the gastroesophageal junction. Water was

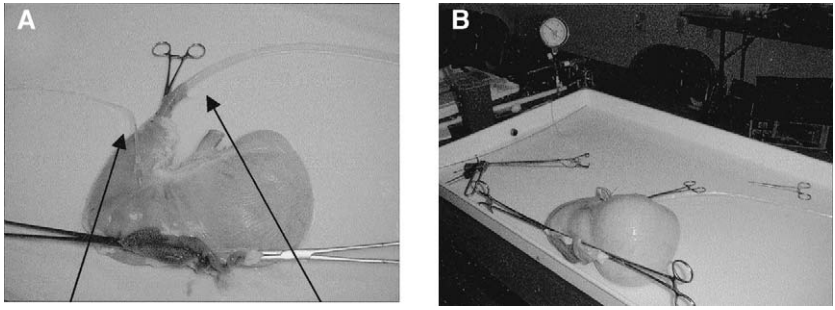

Fig. 3. Efficacy testing set-up: (A) pressure gauge inserted into gastric lumen through anterior wall (*left arrow*), sealed PVC inflow tube shown entering pylorus (*right arrow*); (B) water instilled and gastric pressures recorded.

instilled into the stomach by way of the duodenum. Gastric pressures recorded at the onset of mild (drip) and severe (flow) gastroesophageal reflux were compared pre and post-plication. The plication was then removed, and the process was repeated sequentially at each of the other three quadrants. Gastric pressures were compared between plication sites to determine the optimal site for plication. Esophageal diameters pre and post-plication were measured using a tapered dilator at the gastroesophageal junction.

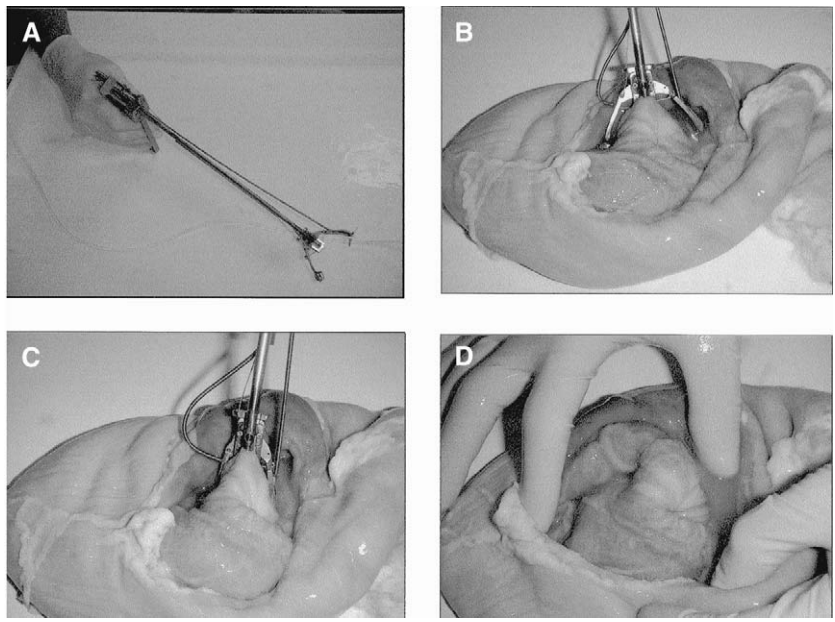

Fig. 4. Bench study method: (A) bench test plication device; (B) tissue retractor advanced to serosa, gastric wall retracted; (C) arms close deploying single, pre-tied implant to secure serosa-to-serosa plication; (D) full-thickness plication.

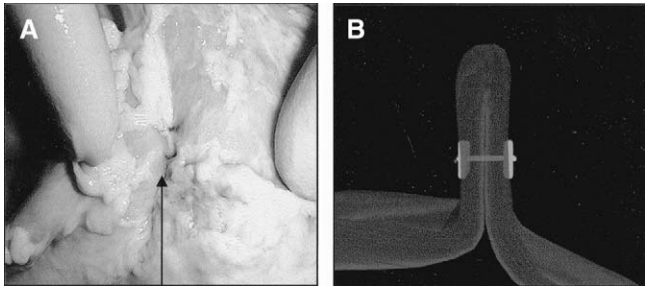

Fig. 5. Full-thickness plication: (A) Serosal observation of suture through full-thickness; (B) schema of ePTFE bolsters and suture securing serosa-serosa plication.

In all four plication locations the full-thickness plication of excised pig stomachs resulted in significant increases in the mean drip and steady flow pressures at which the stomach leaked from the gastroesophageal junction (Table 1). The average gastric yield pressures recorded at the onset of (drip) gastroesophageal reflux and severe reflux (steady flow) increased over eight-fold following plication. The increases in gastric yield pressures were achieved without a significant change in esophageal diameter (Table 2).

Human pilot study

A human feasibility pilot study was conducted to assess the safety and efficacy of endoscopic full thickness plication [11]. Patients with chronic heartburn and pathologic reflux requiring maintenance PPI therapy were recruited. Patients with large hiatal hernias (> 2 cm), grades III and IV esophagitis, and Barrett's esophagus were excluded. The following were assessed at baseline and a 3-, 6-, and 12-month post-plication: GSRS and GERD-HRQL questionnaires, 24-hr pH/manometry and medication use. Endoscopy was performed at baseline 3 and 6 months post placement. All patients received a single, full-thickness plication in the gastric cardia. Plications were placed between the anterior wall and the fundus

Table 1
Effect of full-thickness plication on gastroesophageal reflux

Plication location	Baseline average drip pressure (inches H_20)	Post-plication average drip pressure (inches H_20)	Baseline average steady flow pressure (inches H_20)	Post-plication average steady flow pressure (inches H_20)
Anterior	0.96	3.53*	1.14	4.12**
Fundus	1.35	7.88*	1.46	8.31**
Lesser curvature	0.42	8.56*	0.43	9.22**
Posterior	0.42	9.01*	0.53	13.46**
Average	0.79	7.24*	0.89	8.78**

* $P = < 0.05$ compared with pre-plication average drip pressure.
** $P = 0.001$ compared with pre-plication average steady flow pressure.

Table 2
Esophageal diameter pre and post-plication

Plication location	Baseline average diameter (mm)	Post-plication average diameter (mm)
Anterior	12.05	11.80
Fundus	12.55	12.28
Lesser curvature	12.50	11.89
Posterior	13.16	12.06
Average	12.56	12.00

No significant difference was present between groups.

because it was deemed the safest area, avoiding major branches of the left and right gastric arteries and vagus nerves.

Six men (mean age 31, range 23 to 41) underwent endoscopic full-thickness plication. The mean procedure time was 21 minutes. Twelve-month post-plication, mean GSRS and GERD-HRQL symptom scores improved over 75% (Figs. 6 and 7). Follow-up endoscopy confirmed intact full-thickness plications in all patients. Additionally, the grade of esophagitis was improved in 2 out of the 6 patients at 12 months. On entry, all patients were using daily PPI therapy (requiring 4 pts. twice daily). At six months post-procedure, five of six patients were off PPI therapy. One patient, who did not improve, underwent laparoscopic fundoplication and still had no improvement. Adverse events were mild. mid-epigastric discomfort (n = 2) and difficulty with eructation (n = 1), all resolving spontaneously within one week.

The endoscopic full-thickness plication device is designed to inhibit reflux with a single plication near the gastroesophageal junction. Full-thickness plication of the proximal stomach may improve the competency of the gastroesophageal barrier by restoring the valvular mechanism of the gastroesophageal junction. Other potential mechanisms include alteration of the angle of His, and reduction of the compliance of the gastric cardia and fundus. The procedure is easily and safely performed and, in the human pilot study, has been shown to reduce symptoms and medication use associated with GERD.

It did not interfere with subsequent fundoplication, if required.

In conclusion, a safe and effective endoscopic technique for the treatment of GERD would be extremely valuable. These studies show the effectiveness and safety of full-thickness plication in both animal and human subjects. Based on

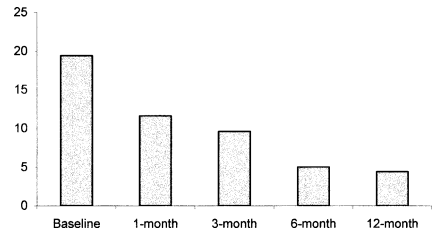

Fig. 6. GSRS mean score.

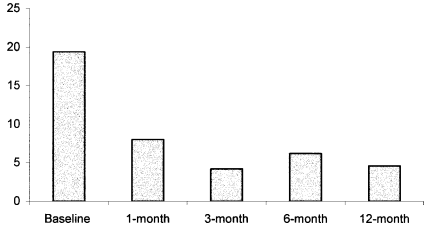

Fig. 7. GERD-HRQL mean score.

these encouraging initial results, a larger multi-center trial is currently in progress to further assess its effectiveness in treating symptomatic GERD.

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