

New Endoscopic Treatments for Gastroesophageal Reflux Disease

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This article reviews the available endoscopic treatments for gastroesophageal reflux disease (GERD). Plicating gastric folds methods, like Bard's EndoCinch™ method (Endoscopic Gastropliation, ELGP method), NDO Surgical's Full-thickness Plicator™ method, and Wilson-Cook Medical's Endoscopic Suturing Device (ESD) method, are used to form new plications in the cardia. Alternatively, thermal tissue remodeling/neurolysis methods, like Curon Medical's Stretta® System, can be used to denature the muscular layer of the lower esophageal sphincter (LES) region. Finally, bulking injection methods, like Boston Scientific's Enteryx® Procedure and Medtronic's Gatekeeper™ Reflux Repair System, can be used to insert a foreign body into the LES region. All six methods resulted in the improvement of symptoms and acid reflux, but only the bulking injection methods caused an improvement of the manometric findings. Nevertheless, the improvement of symptoms and acid reflux seems to be much more important than the improvement of the manometric findings. The overall discontinuation of proton-pump inhibitor (PPI) use was about 70%. Thus, endoscopic treatments for GERD are still in the development phase. The efficacy, safety, durability, cost-effectiveness, indications, and possible combination with other treatments must be thoroughly assessed in randomized controlled trials. If the usefulness of endoscopic treatment is confirmed, however, a new minimally invasive treatment strategy for GERD will have been established. (Ann Thorac Cardiovasc Surg 2005; 11: 146–153)

Key words: gastroesophageal reflux disease, endoscopic treatment

Introduction

The standard treatments for gastroesophageal reflux disease (GERD) consist of the prescription of H₂-receptor antagonists or proton-pump inhibitors (PPI) and antireflux surgery. Minimally invasive laparoscopic or thoracoscopic antireflux surgery replaced open surgery in the 1990s. Recently, another class of minimally invasive treatments using flexible endoscopes has been introduced, broaden-

ing surgical options. These new endoscopic treatments for GERD are reviewed below.

Types of Endoscopic Treatment

According to the latest information presented at the Digestive Disease Week meeting in the USA and recent medical literature, three types of endoscopic treatments are available for GERD. Plicating gastric folds methods, like Bard's EndoCinch™ method (Endoscopic Gastropliation, ELGP method),¹⁾ NDO Surgical's Full-thickness Plicator™ method,²⁾ and Wilson-Cook Medical Endoscopic Suturing Device (ESD) method,³⁾ are used to form new plications in the cardia. Alternatively, thermal tissue remodeling/neurolysis methods, like Curon Medical's Stretta® System,⁴⁾ can be used to denature the muscular layer of the lower esophageal sphincter (LES) region.

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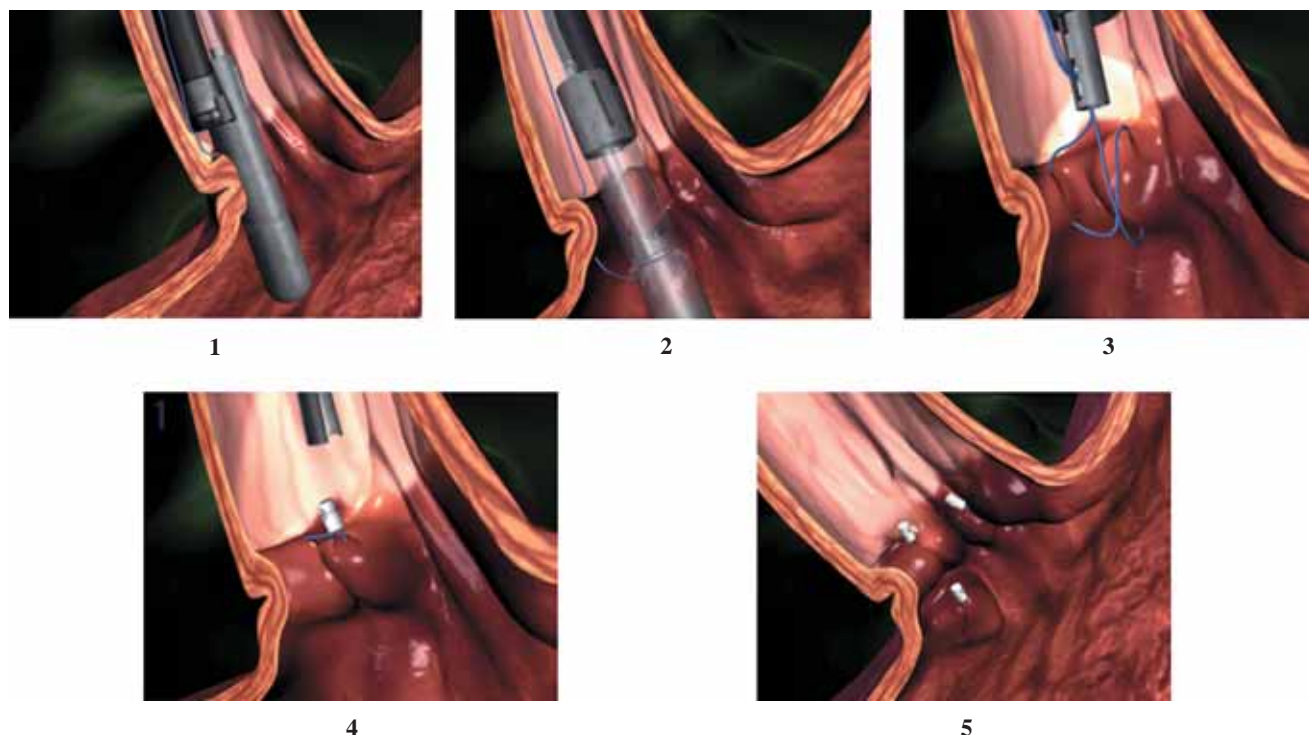


Fig. 1. ELGP procedure.

- 1: The stomach wall is suctioned into the suturing capsule.
- 2: A needle, pusher wire, and suture to which a tag has been attached are inserted into the stomach wall by manipulating the handle of the suturing device.
- 3: Suture ligation is performed using the plastic clip.
- 4: Cutting the sutures is also performed using a one-touch system.
- 5: The completed plication (Permission for use of these illustrations has been obtained from Bard).

Finally, bulking injection methods, like Boston Scientific's Enteryx[®] Procedure⁵⁾ and Medtronic's Gatekeeper[™] Reflux Repair System,⁶⁾ can be used to insert a foreign body into the LES region. The EndoCinch[™], Full-thickness Plicator[™], Stretta[®], and Enteryx[®] methods have been approved by the American Food and Drug Administration (FDA) and have been used throughout the USA and Europe. In Japan, only a clinical trial for the ELGP method is presently in progress.

ELGP Method

An endoscope is inserted into the stomach and as much fluid as possible is aspirated. An overtube is then inserted along with the first endoscope (Fig. 1).¹⁾ A second endoscope equipped with the EndoCinch[™] suturing device is inserted into the esophagus through the overtube to a point 1 cm caudal to the squamocolumnar junction (Z line). The gastric wall is then suctioned into the capsule of the suturing device by the application of a negative pressure

of more than 400 mmHg. A needle, a pusher wire, and a 3-0 thread with a suture tag are passed through the gastric wall by controlling the device's handle. After aspiration is stopped, the endoscope with the thread is pulled out, and the first stitch is completed. The capsule is then set for the next stitch. The second stitch is placed about 60 degrees away from the first stitch. The knot is easily tied utilizing the clip of the delivery system, and the first plication is completed. If necessary, a second, third, or fourth plication may also be performed.

Filipi et al. reported the results of a six-month clinical trial using the EndoCinch[™] method,⁷⁾ Mahmood et al. reported the results of a 12-month clinical trial,⁸⁾ and Chen et al. reported the results of a 24-month clinical trial.⁹⁾ The heart burn (HB) (0-96) and regurgitation (0-3) scores improved after the procedure, and these improvements persisted for up to 24 months. Adverse events like pharyngalgia (31-32% of cases), chest pain (16-23% of cases), and abdominal pain (14-16% of cases) were minor, so this method was regarded as safe. Rothstein et al.

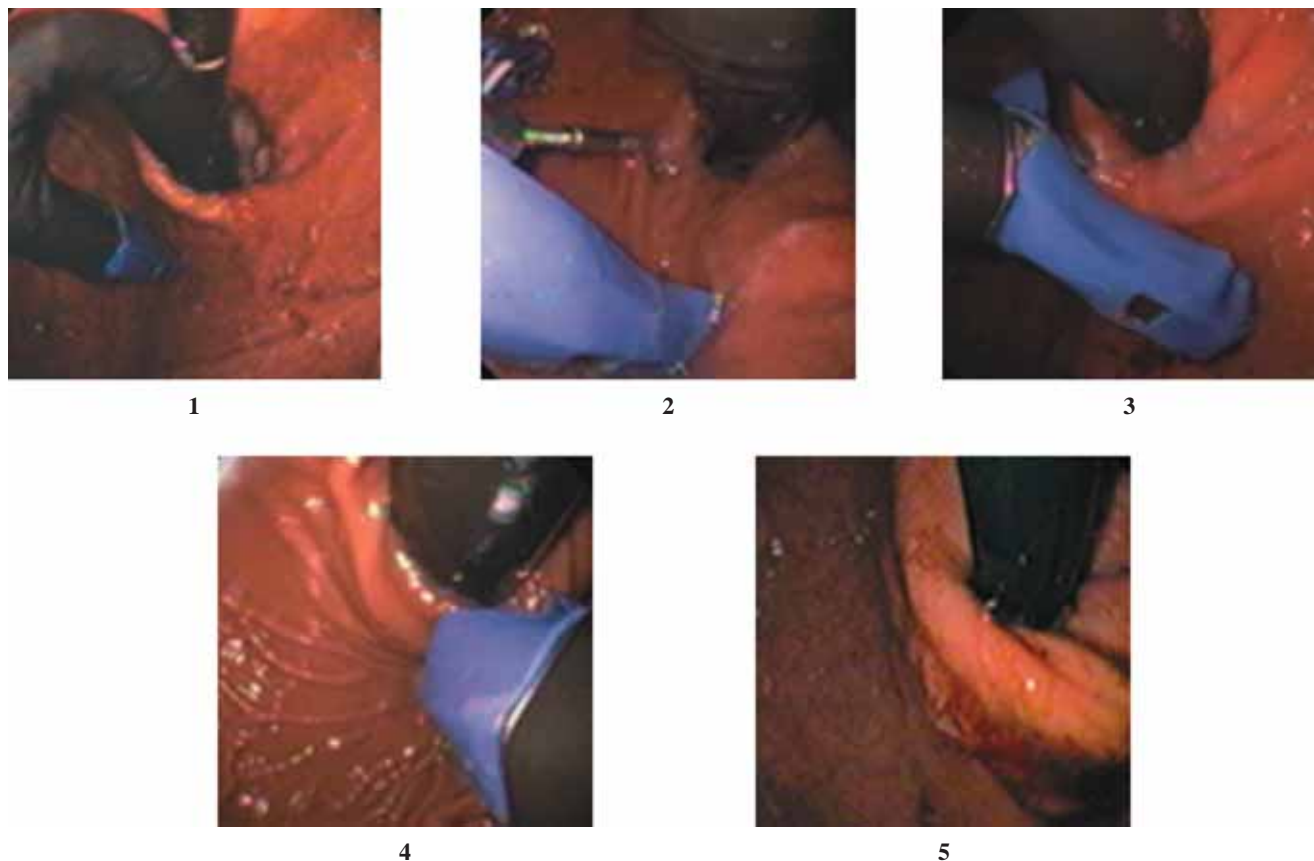


Fig. 2. Full-thickness Plicator procedure.

- 1: An accessory endoscope is angled to enable the cardiac region to be observed.
- 2: The arm of the device is opened, and the Tissue Retractor is rotated and implanted into the stomach wall.
- 3: The stomach wall is fully retracted.
- 4: The arm is closed, the needles and threads are inserted into the stomach wall, and suturing and fixation are performed simultaneously.
- 5: The completed plication (Permission for use of these photos has been obtained from NDO Surgical).

reported an excellent clinical trial with a randomized, sham-controlled, blinded single-center design.¹⁰ Although the three-month observation period was relatively short, the decreased frequencies of HB and acid reflux and the reduction in antacid medication use in the ELGP group may be cautiously interpreted as indicating the usefulness of this method.

In a report by Filipi et al., the manometric findings and the endoscopic grade of esophagitis showed no signs of improvement 6 months after ELGP, although the 24-hour pH monitoring results showed an improvement in acid reflux.⁷ In a report by Mahmood et al., the manometric findings did not change, but the 24-hour pH monitoring results improved 3 months after ELGP.⁸ Although a few other reports have been made, the present consensus that ELGP improves acid reflux but does not influence the motor function of the esophagus.

Mahmood et al. reported that PPI use was discontin-

ued in 64% of patients at 6 and 12 months after ELGP.⁸ Ponchon et al. reported that PPI use was discontinued in 75%, 67%, 53%, and 50% of patients at 1, 3, 6, and 12 months after ELGP.¹¹ These values are slightly lower than those for other therapies.

Full-thickness Plicator Method

The full-thickness PlicatorTM method creates layered sutures of the stomach wall in the cardiac region using suturing equipment at the tip of a main endoscope, while a thin accessory endoscope inserted into the main endoscope is used to observe the suturing procedures. (Fig. 2).² A pilot study of six cases examined the safety of this method, and a multi-institutional, cooperative clinical trial enrolled 64 cases.¹² Six months after treatment, pH normalization was observed in 30% of the patients and PPI use was discontinued in 74% of the patients.

However, esophageal manometric findings, like the LES pressure, did not change postoperatively. Another report stated that PPI use was discontinued in 68% of patients at 12 months after the operation.¹³⁾

Regarding adverse effects, 41% of patients experienced pharyngalgia, 20% experienced abdominal pain, 17% experienced chest pain, 17% experienced abnormal digestive tract symptoms, 14% experienced ructus, 11% experienced dysphagia, and 6% experienced nausea. However, two cases (3%) of dyspnea caused by the overtube insertion, one case (1.6%) of pneumothorax thought to be caused by an elevation in intrapleural pressure as a result of breath holding, one case (1.6%) of pneumoperitoneum (1.6%) thought to be caused by the exsorption of intragastric inflating air from the stomach walls, one case (1.6%) of gastric perforation, and one case (1.6%) of mucosal injury occurred. Thus, the safety of this procedure must be further examined. Since the sutures placed by this system encompass the entire gastric wall, suture defluxion is unlikely; thus, the sutures are expected to be quite durable, making this method a promising strategy for the treatment of GERD.

Endoscopic Suturing Device Method

The principle behind the ESD method resembles that of the EndoCinch™ method. The outside of the endoscope is equipped with an operation tube with an inside diameter of 6 mm, and the suturing is performed using a Sew-Right Device. The tip of this instrument consists of two needle receptacles containing two needles connected by a 2-0 polyester thread. The stomach wall is suctioned, a needle is inserted into the wall, and the free end of the thread is pulled into the needle receptacle; the second needle is then inserted and the free end of the thread is similarly pulled. The two ends of the thread are then removed from the patient's body (Fig. 3). Next, a Ti-Knot Device, is used to tightly bind the two ends of the thread and secure them with a titanium clip. In this manner, a plication is formed.³⁾

Rosen et al. used this procedure to treat two cases and reported an improvement in the patients' symptoms six months after the operation. Liu et al. used this procedure to treat 10 cases and reported an improvement in the patients' symptoms, a reduction in acid reflux, and a reduction in PPI use.¹⁴⁾ Schilling et al. treated 11 cases and noted transient adverse effects in 27% of the cases. Moreover, the sutures had slipped off and disappeared in 27% of the patients four weeks after the operation. Early su-

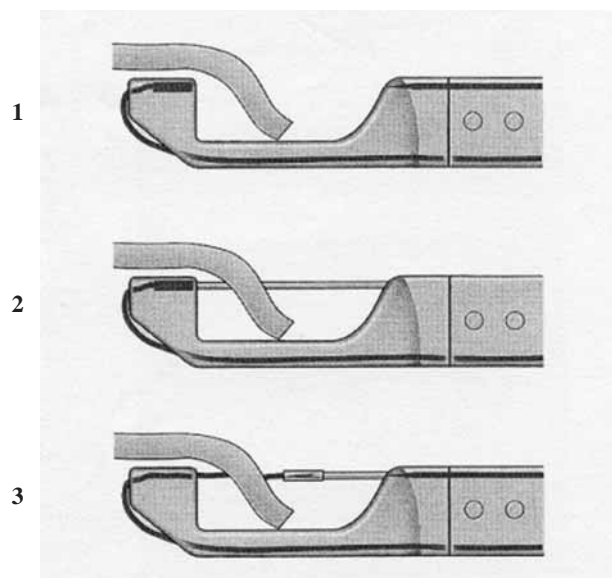


Fig. 3. Endoscopic Suturing Device (ESD) method procedure.

- 1: The stomach wall is suctioned.
- 2: The needle is inserted through the tissue.
- 3: The needle is retracted into the needle receptacle, pulling the thread through the tissues (Permission for use of these photos has been obtained from Elsevier).

ture slippage appears to be a problem with this technique.¹⁵⁾ Saeed et al. treated 19 cases, and reported the disappearance of symptoms in 47% of the patients 12 months after the operation.¹⁶⁾ PPI use was discontinued in 42% of the patients; among patients with three or more sutures, however, PPI use was discontinued in 88% of the patients. Thus, three or more sutures may be required for this procedure.¹⁶⁾ Nevertheless, the results of further clinical trials in a larger number of patients are needed before making any definite conclusions regarding the effectiveness of this technique.

Stretta Method

The Stretta® System employs a special balloon equipped with four needle electrodes (22 G, 5.5 mm) that is extended into the gastroesophageal junction. Next, the electrodes are inserted into the esophagus or stomach walls, and electricity is passed through the electrode creating radiofrequency (RF) energy. Automatic thermoregulation maintains the temperature of the electrodes at 85.⁴⁾ First, RF energy is applied to four points located 1 cm cephalad to the Z line. Next, the electrodes are rotated 45 degrees, and RF energy is applied to four more points at the same level. In this manner, RF energy is applied to a total

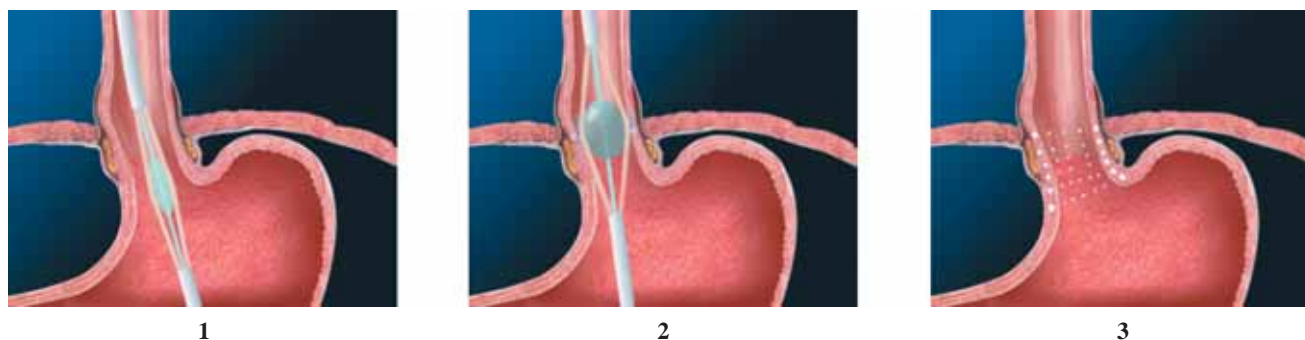


Fig. 4. Stretta procedure.

- 1: The Stretta[®] Catheter is guided using a guide wire and inserted into the stomach.
- 2: RF energy is applied to a total of eight points at a level 1 cm caudal to the Z line.
- 3: View after the completion of the operation. RF energy is applied to eight points at 4 different levels and at 12 points on 2 different levels for a total of 56 points (Permission for use of these illustrations has been obtained from Curon Medical).

of eight points at the same level. This procedure is repeated at three more levels located at intervals of 0.5 cm moving caudally. Next, the deflated balloon is inserted further into the stomach and inflated once again with 25 ml of air; the balloon is then pulled cephalad until it is caught in the cardia. RF energy is then applied to 12 points at this level. Finally, the balloon is inflated with 22 ml of air, and RF energy is applied to 12 points at a level 1 cm towards the cephalad side (Fig. 4).

Triadafilopoulos et al.¹⁷⁾ reported good results in 47 cases six months after treatment. Symptoms, acid reflux, and esophagitis improved significantly, and the discontinuation of PPI use was relatively high (87% of cases). However, no changes in the motor function of the esophagus, as evaluated by measuring the LES pressure and length, were seen. Slight complications arose in three cases.¹⁷⁾ Furthermore, this group also reported the 12-month follow-up results of a multi-institution cooperative clinical trial with 118 enrolled cases. The average HB score improved from 4 before treatment to 1 after, the GERD score improved from 27 to 9, and patient satisfaction improved from 1 to 4.¹⁸⁾ In addition, pH monitoring showed a reduction in acid reflux, and PPI dependence decreased from 88.1% to 30%. Although adverse effects were seen in 8.6% of the cases, intensive treatments were not required. Perforation, infection, or death did not occur in this series. Wolfsen et al. reported a clinical trial of 558 cases, and concluded that the technique was effective for enabling the use of anti-acid secretory agents to be discontinued for one year or more.¹⁹⁾ Houston et al. enrolled 41 cases in a clinical trial, and reported an improvement in the patients' symptoms, a reduction of acid reflux, and the discontinuation of PPI use in 65% of

patients 6 months after treatment.²⁰⁾ Moreover, according to the results of a clinical trial with 130 enrolled cases, the average HB score improved from 3.7 before treatment to 0.7 at 24 months after treatment, the average GERD-Health Related Quality of Life (GERD-HRQL) score improved from 28.4 to 4.1, and average patient satisfaction improved from 1.4 to 4.4.²¹⁾ Therefore, this procedure may be effective for up to 24 months, and is considered to be safe.

Enteryx Method

In the Enteryx[®] Procedure, an infusion of 6-8 ml of 8% ethylene vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO) with tantalum as an X-ray contrast medium is slowly administered at a rate of 1 ml/min or less to the muscle or deep submucosal layers at a point about 1-2 mm caudal to the Z line using a 23-gauge needle (4 mm)⁵⁾ (Fig. 5). The polymerization of the EVOH is thought to alter the function of the gastroesophageal junction. A pilot study with 15 cases confirmed the continuous elevation of the LES pressure and the safety of the procedure in general.²²⁾

Next, a multi-institutional, cooperative clinical trial of 85 cases showed that the average GERD-HRQL improved from 24.0 before treatment to 4.0 at 6 months after treatment.²³⁾ The rate of PPI discontinuation 6 months after treatment was 74%, and a reduction in acid reflux (as shown by pH monitoring) and the extension of the LES length (as shown by an esophageal manometric study) were seen. Critical adverse effects, other than transient chest pain, were not seen. In 80.3% of the patients, the treatment was effective for at least 12 months. PPI discontinuation was seen in 87.7% of the patients. Thus, this

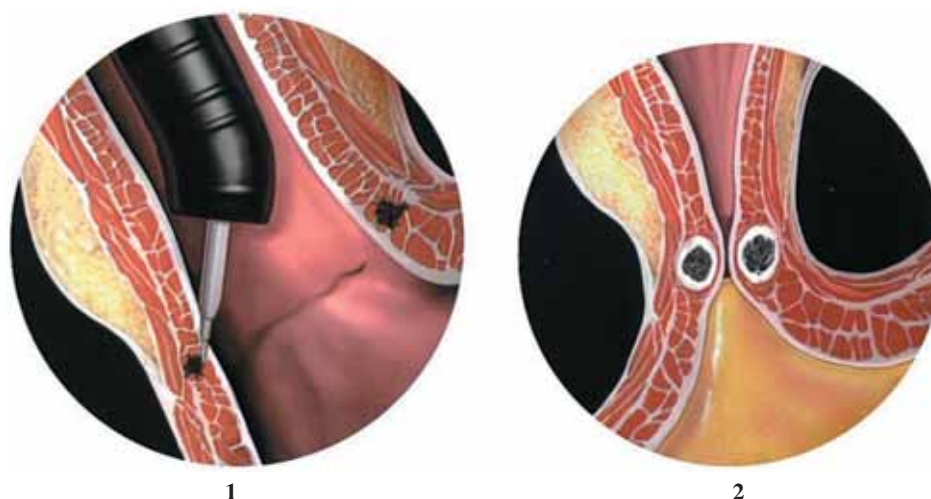


Fig. 5. Enteryx procedure.

1: Enteryx[®] is infused into the muscular and submucosal layers at a point about 1-2 mm caudal to the Z line.

2: EVOH polymerizes (Permission for use of these illustrations has been obtained from Boston Scientific).

treatment was considered effective when the volume of infused Enteryx[®] was 5 ml or more.²⁴ Although the acid reflux to the esophagus decreased significantly, the grade of esophagitis did not change. As a complication, transient retrosternal pain was seen in 91.8% of the patients. The treatment was thought to be effective for at least 12 months.

Gatekeeper Method

The Gatekeeper[™] Reflux Repair System utilizes a polyacrylonitrile-based hydrogel (HYPAN) rod (1.5 mm×18 mm) that is implanted in the submucosal layer on the oral side of the esophagogastric junction. An overtube is inserted, and physiological saline is injected into the submucosal layer using a special tube, prior to the implantation of the HYPAN prosthesis⁶ (Fig. 6). Over the next 24 hours, the prosthesis swells, narrowing the luminal diameter of the lower esophagus. A multi-institutional, cooperative clinical trial of 68 cases reported that the prosthesis remained intact one and six months after treatment in 80.4% and 70.4% of the patients, respectively, acid reflux decreased significantly, and the average LES pressure significantly increased from 8.8 mmHg to 13.8 mmHg. The average GERD-HRQL also improved from 24.0 to 5.0 at six months after the treatment.^{25,26}

The critical adverse effects consisted of a pharyngeal perforation caused by the insertion of the overtube in one case and persistent nausea in one case. Gabbrielli et al. reported that PPI use was discontinued in 77 and 46% of the patients at 6 and 24 months after treatment, respectively. The rate of the prosthesis survival 6 months after treatment was 65%. The prosthesis is thought to be dislodged over time, accounting for the reduction in PPI dis-

continuation.²⁷ Since the durability of the prosthesis inserted under the mucosa remains a problem, long-term follow up is required. If the prosthesis becomes unnecessary, it can be endoscopically removed.

Summary of Endoscopic Treatment Results

All six endoscopic methods described in this review resulted in the improvement of symptoms and acid reflux, but only the bulking injection methods (Enteryx[®] and Gatekeeper[™]) caused an improvement of the manometric findings (Table 1). Nevertheless, an improvement of the manometric findings may not be necessary if the patients' symptoms and acid reflux are improved. PPI use was discontinued after six months in 53-74% of patients being treated with the plicating gastric folds methods, 65-87% of patients treated with thermal tissue remodeling/neurolysis methods, and 74-77% of patients treated with bulking injection methods. The overall discontinuation of PPI use, therefore, was about 70%. Long-term follow-up studies to investigate durability are now required. Moreover, the possibility that the incidence of complications may decrease as endoscopists become more proficient at using these new methods should also be examined.

Endoscopic treatments for GERD continue to be examined and refined in studies performed throughout the world, although only one clinical trial for the ELGP method is presently underway in Japan. The efficacy, safety, durability, cost-effectiveness, indications, and combination must be examined in long-term follow-up studies. If the efficacy of endoscopic treatment is confirmed and approved in the future, a new minimally invasive treatment strategy for GERD will have been established.

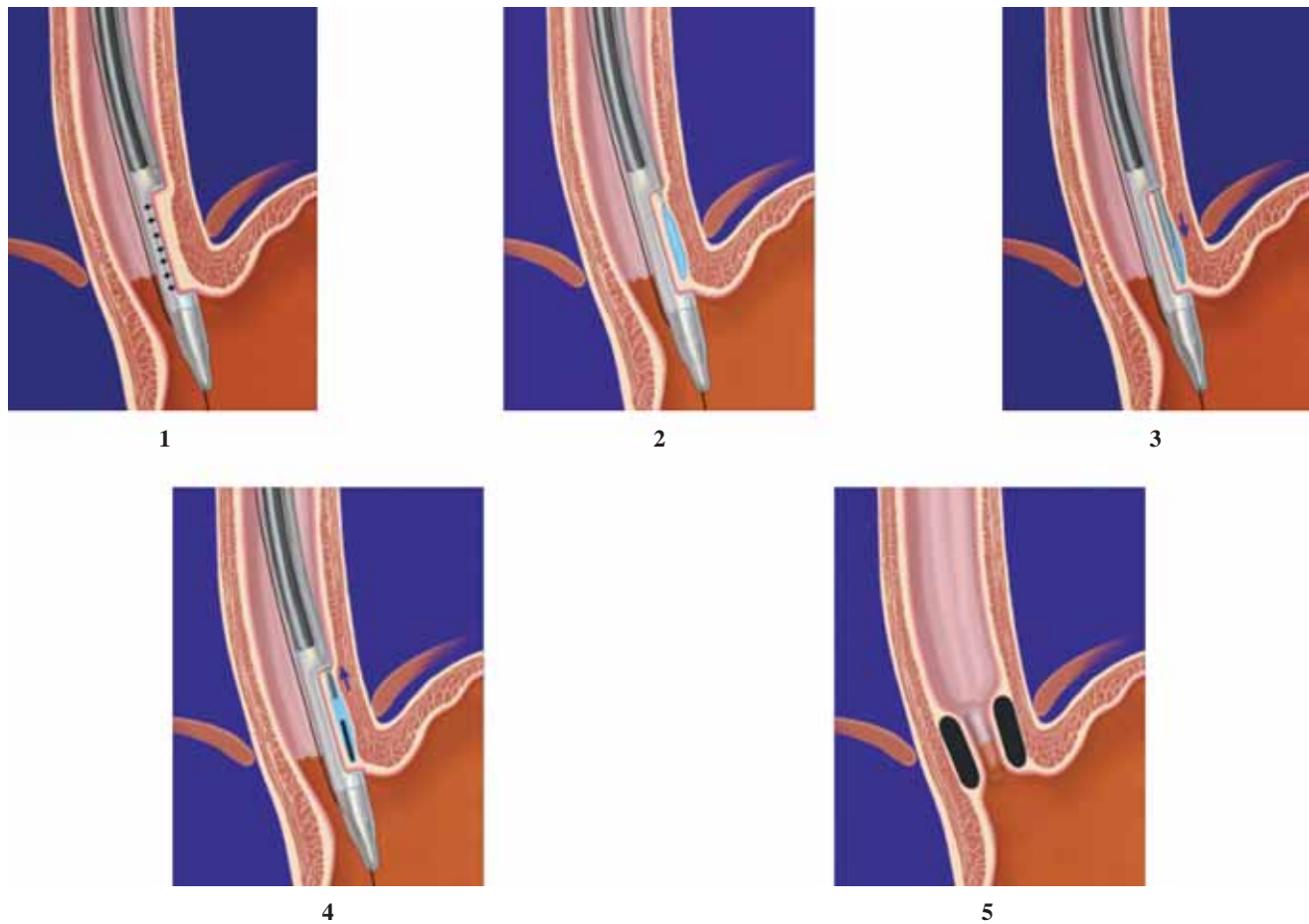


Fig. 6. Gatekeeper procedure.

- 1: The esophagus wall is aspirated.
- 2: Normal saline is injected into the submucosal layer.
- 3: A pocket is created in the submucosal layer.
- 4: The HYPAN prosthesis is implanted in the pocket.
- 5: View after the completion of the operation (Permission for use of these illustrations has been obtained from Medtronic).

Table 1. Summary of endoscopic treatment results for gastroesophageal reflux disease

Method	Improvement of symptoms	Improvement of acid reflux	Improvement of manometric findings	PPI-off rate	
				6 mo.	12 mo.
ELGP	○	○	×	64%	64%
Full-thickness Plicator™	○	○	×	53%	50%
ESD	○	–	–	–	42%
Stretta®	○	○	×	87%	–
Enteryx®	○	○	○	65%	–
Gatekeeper™	○	○	○	74%	–
Gatekeeper™	○	○	○	77%	–

PPI-off rate: percentage of patients in whom proton-pump inhibitor use was discontinued.

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