

Efficacy of endoluminal gastroplication in Japanese patients with proton pump inhibitor-resistant, non-erosive esophagitis

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Abstract

AIM: To evaluate the efficacy, safety, and long-term outcomes of endoluminal gastroplication (ELGP) in patients with proton pump inhibitor (PPI)-resistant, non-erosive reflux disease (NERD).

METHODS: The subjects were NERD patients, diagnosed by upper endoscopy before PPI use, who had symptoms such as heartburn or reflux sensations two or more times a week even after 8 wk of full-dose PPI treatment. Prior to ELGP, while continuing full-dose PPI

medication, patients' symptoms and quality of life (QOL) were assessed using the questionnaire for the diagnosis of reflux disease, the frequency scale for symptoms of gastro-esophageal reflux disease (FSSG), gastrointestinal symptoms rating scale, a 36-item short-form. In addition, 24-h esophageal pH monitoring or 24-h intraesophageal pH/impedance (MII-pH) monitoring was performed. The Bard EndoCinch™ was used for ELGP, and 2 or 3 plications were made. After ELGP, all acid reducers were temporarily discontinued, and medication was resumed depending on the development and severity of symptoms. Three mo after ELGP, symptoms, QOL, pH or MII-pH monitoring, number of plications, and PPI medication were evaluated. Further, symptoms, number of plications, and PPI medication were evaluated 12 mo after ELGP to investigate long-term effects.

RESULTS: The mean FSSG score decreased significantly from before ELGP to 3 and 12 mo after ELGP (19.1 ± 10.5 to 10.3 ± 7.4 and 9.3 ± 9.9 , $P < 0.05$, respectively). The total number of plications decreased gradually at 3 and 12 mo after ELGP (2.4 ± 0.8 to 1.2 ± 0.8 and 0.8 ± 1.0 , $P < 0.05$, respectively). The FSSG scores in cases with no remaining plications and in cases with one or more remaining plications were 4.4 and 2.7, respectively, after 3 mo, and 2.0 and 2.8, respectively, after 12 mo, showing no correlation to plication loss. On pH monitoring, there was no difference in the percent time pH < 4 from before ELGP to 3 mo after. Impedance monitoring revealed no changes in the number of reflux episodes or the symptom index for reflux events from before ELGP to 3 mo after, but the symptom sensitivity index decreased significantly 3 mo after ELGP (16.1 ± 12.9 to 3.9 ± 8.3 , $P < 0.01$). At 3 mo after ELGP, 6 patients (31.6%) had reduced their PPI medication by 50% or more, and 11 patients (57.9%) were able to discontinue PPI medication altogether. After 12 mo, 3 patients (16.7%) were able to

reduce the amount of PPI medication by 50% or more, and 12 patients (66.7%) were able to discontinue PPI medication altogether. A high percentage of cases with remaining plications had discontinued PPIs medication after 3 mo, but there was no difference after 12 mo. No serious complications were observed in this study.

CONCLUSION: ELGP was safe, resulted in significant improvement in subjective symptoms, and allowed less medication to be used over the long term in patients with PPI-refractory NERD.

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Key words: Endoluminal gastroplication; Esophageal pH; Gastro-esophageal reflux disease; Non-erosive reflux disease; Proton pump inhibitor-resistant

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INTRODUCTION

Non-erosive reflux disease (NERD) refers to a syndrome that is characterized by complaints of reflux symptoms such as heartburn without endoscopic evidence of mucosal injury^[1]. It accounts for more than half of gastroesophageal reflux disease (GERD) cases in Japan, as it does in Europe and the United States^[2]. NERD and erosive GERD cannot be distinguished by the severity of symptoms or their frequency, and they are equally characterized by compromised quality of life (QOL)^[3,4]. Proton pump inhibitors (PPIs), which are first-line drugs for GERD, are less effective for NERD than they are for erosive GERD^[5]. NERD symptoms are often not amenable to treatment with oral medication. It was recently proposed that NERD is not just a milder form of reflux disease but a group of symptoms with pathophysiologic mechanisms that differ from those of erosive GERD^[6]. It has been reported that a number of etiologies may contribute to the symptoms of heartburn, including motor events, reflux of nonacidic gastric contents, minute changes in intraesophageal pH, visceral hypersensitivity, and emotional or psychological abnormalities^[7-9]. However, many of the details involved in its mechanism remain unknown. The recent use of ambulatory multichannel intraluminal impedance-pH (MII-pH) monitoring has made it possible to learn about various symptom-inducing factors that could not be determined by conventional pH monitoring alone^[10], and it has elucidated the patho-

physiology involved in PPI-refractory NERD. It is now believed that factors other than gastroesophageal reflux or non-acid reflux are involved in its pathophysiology^[11].

The surgical treatment of erosive GERD originated with Allison *et al*^[12] in 1951. Laparoscopic fundoplication (Nissen fundoplication or Toupet fundoplication) is now widely used and is reportedly useful over the long-term^[13,14]. However, its inherent invasive nature as a surgical procedure remains problematic. In response to the inconvenience and non-compliance associated with drug use, as well as the complications associated with laparoscopic surgery, a number of endoscopic techniques have been developed since 2000, primarily in Europe and the United States, as less invasive but effective methods. In Japan, only endoluminal gastroplication (ELGP) using the Bard EndoCinchTM (C. R. Bard, Murray Hill, NJ, United States) has been covered by national health insurance (K667-3: 12 000 points). This procedure permits less invasive fundoplication to be accomplished using an endoscope, and it has been reported to be useful over the long term^[15]. However, it is used in cases in which PPI treatment is effective. The efficacy of endoscopic treatment in PPI-resistant GERD not amenable to treatment with oral medication has not yet been sufficiently studied.

Until recently, NERD has been assumed to be milder than erosive GERD, and NERD has not been considered suitable for surgical treatment. However, surgical fundoplication is now performed in cases of NERD not amenable to drug treatment, and its efficacy is becoming increasingly clear^[16,17]. However, the efficacy of endoscopic treatment in NERD patients has not been studied. Therefore, the efficacy, safety, and long-term course of ELGP as endoscopic treatment in patients with PPI-resistant NERD, who are the most intractable of NERD patients, were studied.

MATERIALS AND METHODS

This was a prospective study conducted at Aichi Medical University Hospital. Nineteen subjects were enrolled between March 2005 and June 2009 (14 males and 5 females; average age 53.0 ± 4.3 years). The study was approved by the Aichi Medical University School of Medicine Ethics Review Board and was conducted with the written informed consent of patients who had been given a full explanation of the study. The subjects were NERD patients, diagnosed by upper endoscopy before PPI use, who had symptoms such as heartburn or reflux sensations two or more times a week even after 8 wk of full-dose PPI-treatment (i.e., 30 mg of lansoprazole, 20 mg of rabeprazole, or 20 mg of omeprazole per day). The following exclusion criteria were used: < 18 years of age; hiatal hernia (≥ 2 cm); erosive GERD (Los Angeles Grade A or higher) before PPI use; Barrett's esophagus; gastroesophageal varices; past history of gastroesophageal surgery; gross obesity (body mass index > 40 kg/m²); esophageal stenosis; dysphagia; and primary esophageal motility disorders diagnosed by intraesophageal manom-

etry (Polygraf ID, Sierra Scientific, Los Angeles, CA, United States).

Interview and tests

Prior to ELGP, while continuing full-dose PPI medication, patients were assessed for reflux symptoms based on the questionnaire for the diagnosis of reflux disease (QUEST)^[18] and the frequency scale for symptoms of GERD (FSSG)^[19]. The gastrointestinal symptoms rating scale (GSRS) was used as an indicator of gastrointestinal symptoms, and 36-item short-form (SF-36)^[20] interview was conducted as an assessment of the activity index. In addition, 24-h esophageal pH monitoring (Digitrapper MK III, Synectics Medical, Los Angeles, CA, United States) or 24-h transesophageal pH/impedance monitoring (Sleuth® multi-impedance pH monitoring system, Sandhill Scientific, Highlands Ranch, CO, United States)^[10] was performed. After ELGP, all acid reducers were temporarily discontinued, and medication was resumed depending on the development and severity of symptoms.

Reflux symptoms were assessed by the QUEST and FSSG interviews at 3 and 12 mo after ELGP. The GSRS and SF-36 interviews, as well as 24-h esophageal pH monitoring or 24-h intraesophageal pH/impedance monitoring, were performed after 3 mo. Analysis was performed using the automatic analysis program BioVIEW Analysis® (version 5.3.4; Sandhill Scientific, Inc.)^[21] to compare the symptom index (SI), the symptom sensitivity index (SSI), number of reflux episodes, and number of symptom events. SI is defined as the number of symptoms associated with reflux divided by the total number of symptoms during 24 h, and it primarily assesses the specificity of a patient's reflux symptoms; it is considered positive if more than 50% of the symptoms are associated with reflux^[22]. SSI is defined as the number of reflux events associated with symptoms divided by the total number of reflux events in 24 h, and it quantifies the subject's sensitivity for reflux; it is considered positive if more than 10% of the reflux events are associated with symptoms^[23]. Upper endoscopy was also performed 3 and 12 mo after ELGP to compare the number of remaining plications.

ELGP method

The Bard EndoCinch™ (C. R. Bard) was used for endoluminal gastroplication. After the esophagus had been examined by routine endoscopy, an endoscope with a capsule-shaped plication device (with a side hole) mounted at the tip was brought to the level of the squamocolumnar junction through the over-tube, where the side hole was brought into close contact to draw the mucosa into the capsule with at least 400 mmHg of air suction. After it had been confirmed that all tissue had been drawn in, a puncture needle with 3-0 nonabsorbable suture attached (suture tag), which had been inserted into the biopsy channel, was passed through. The suction pressure was released, and the capsule was carefully rotated away from the stitches side. A suture tag was again set up in the endoscope, and a second set of stitches was placed follow-

Table 1 Patients' baseline characteristics

Characteristics	Value
Patients (n)	19
Age, yr (range)	53.0 ± 4.3 (25-82)
Sex (male:female)	14:5 (73.7%:26.3%)
Body mass index (kg/m ²) (range)	22.3 ± 0.4 (21.5-23.5)
Hiatal hernia, n (%)	18 (94.7)
PPI medication, n (%)	19 (100)

PPI: Proton pump inhibitor.

ing the same procedure at a position rotated 30 to 60 degrees away from the first set of stitches. The two sutures made a plication using a suturing device (knotting device) that had been inserted into the biopsy channel of a separate endoscope, and plication was completed by plicating the tissue in the form of a pouch. The second and third plications were performed in either a linear or circumferential manner, or a combination of the two, depending on the available area within the gastro-esophageal junction and position preference^[23-27].

Statistical analysis

Data are shown as the means ± SD. Analysis was based on Wilcoxon's signed-rank test, the Kruskal Wallis test, and the Steel-Dwass or χ^2 test. A significant difference was defined as $P < 0.05$.

RESULTS

Table 1 shows the characteristics of the 19 subjects enrolled in this study. One patient died of an accident during long-term follow-up. Therefore, only 18 subjects completed long-term follow-up for 12 mo. The QUEST questionnaire and FSSG questionnaire were each collected from 19 (100%) and 12 (66.7%) subjects 3 and 12 mo after ELGP, respectively. Ten subjects consented to GSRS, SF-36, and 24-h intra-esophageal pH/impedance monitoring. Six patients failed to attend for endoscopy at 12 mo. No serious complications were observed in this study. Minor hemorrhage due to mucosal injury during the ELGP procedure was observed in only 2 cases.

The mean QUEST score did not change, but the mean FSSG score decreased significantly, from before ELGP to 3 and 12 mo after. The total number of plications decreased significantly at 3 and 12 mo after ELGP (Table 2).

On 24-h esophageal pH monitoring, there was no difference in the percent time pH < 4 from before ELGP to 3 mo after. Impedance monitoring revealed no changes in the number of reflux episodes or the symptom index (SI) for reflux events from before ELGP to 3 mo after, but the number of symptom events and SSI decreased significantly 3 mo after ELGP (Table 3, Figure 3).

At 3 mo after ELGP, 2 patients were still on full-dose PPI (10.5%), 6 patients had reduced their PPI medication by 50% or more (31.6%), and 11 patients were able to discontinue PPI medication altogether (57.9%). After 12 mo, 2 patients were still on full-dose PPI (11.1%), 3 pa-

Table 2 QUEST score, frequency scale for symptoms of the gastro-esophageal reflux disease score, and plication count after endoluminal gastroplication

	Baseline (<i>n</i> = 19)	3 mo (<i>n</i> = 19)	12 mo (<i>n</i> = 12)
QUEST score	5.7 ± 4.1	4.2 ± 4.5	2.5 ± 4.2
FSSG score	19.1 ± 10.5	10.3 ± 7.4 ^a	9.3 ± 9.9 ^a
Plication count	2.4 ± 0.8	1.2 ± 0.8 ^a	0.8 ± 1.0 ^a

^a*P* < 0.05 *vs* baseline by Kruskal Wallis test plus Steel-Dwass test. QUEST: Questionnaire for the diagnosis of reflux disease; FSSG: Frequency scale for symptoms of gastro-esophageal reflux disease.

Table 3 Twenty-four hour intra-esophageal ambulatory multichannel intraluminal impedance-pH monitoring data at baseline and 3 mo after endoluminal gastroplication

	<i>n</i>	Baseline	3 mo
24-h intra-esophageal time pH < 4 (%)	18	4.1 ± 4.0	10.4 ± 19.2
Numbers of reflux events, %	10	100.3 ± 16.1	79.5 ± 13.5
Symptom index (SI), %	10	70.9 ± 9.2	79.0 ± 10.1
Symptom sensitivity index (SSI), %	10	16.1 ± 12.9	3.9 ± 8.3 ^b
Number of symptom events, %	10	27.2 ± 5.9	7.3 ± 5.2 ^b

^b*P* < 0.01 *vs* 3 mo after endoluminal gastroplication by Wilcoxon's signed rank test.

tients had reduced their PPI medication by 50% or more (16.7%), and 12 patients were able to discontinue PPI medication altogether (66.7%) (Figure 1).

The GSRS total score, reflux score, abdominal pain score, and indigestion score had improved significantly from before ELGP to 3 mo after. Prior to ELGP, the SF-36 scores were all below the national standard scores. After 3 mo, physical functioning and overall health had improved significantly (Table 4).

Three months after ELGP, one or more plications remained in 80%, and two or more remained in 40%. After 12 mo, one or more plications remained in 43%, and it was confirmed that the sloughing off of plications was followed by scar formation in 75%. Therefore, the correlation of medication dose to loss of antireflux function and symptoms induced by the sloughing off of plications was studied. The FSSG score in cases with no remaining plications and in cases with one or more remaining plications was 4.4 and 2.7, respectively, after 3 mo, and 2.0 and 2.8, respectively, after 12 mo, revealing no correlation to plication loss (Figure 2A). After 3 mo, 33.3% and 66.7%, respectively, had discontinued PPI medication, whereas 83.3% had done so in both groups after 12 mo. A high percentage of cases with remaining plications had discontinued PPIs medication after 3 mo, but there was no difference after 12 mo (Figure 2B).

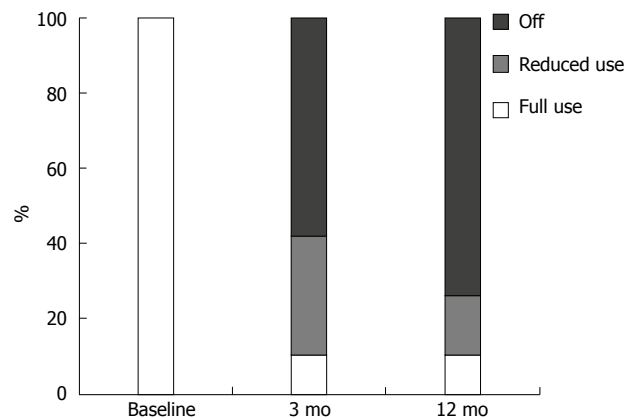
DISCUSSION

This is the first report showing that ELGP is useful in improving symptoms in Japanese PPI-resistant NERD

Table 4 Gastrointestinal symptoms rating scale and 36-item short-form at baseline and 3 mo after endoluminal gastroplication

	Baseline (<i>n</i> = 10)	3 mo (<i>n</i> = 10)
GSRS scale		
Overall	2.5 ± 0.8	1.8 ± 0.4 ^a
Acid reflux	3.3 ± 1.5	2.1 ± 0.7 ^a
Abdominal pain	2.7 ± 1.4	1.8 ± 0.9 ^a
Indigestion	2.6 ± 1.0	1.6 ± 0.8 ^a
Diarrhea	1.8 ± 0.9	1.4 ± 0.6
Constipation	2.3 ± 1.3	1.9 ± 1.3
SF-36 scale		
Physical functioning	46.6 ± 15.8	53.7 ± 3.8 ^a
Role physical	36.9 ± 20.0	48.7 ± 15.7
Bodily pain	40.5 ± 16.7	52.7 ± 8.3
General health	43.2 ± 7.8	48.8 ± 6.2 ^a
Vitality	42.9 ± 12.7	50.6 ± 6.7
Social functioning	44.0 ± 12.6	47.2 ± 9.9
Role emotional	37.2 ± 19.4	47.7 ± 13.7
Mental health	46.3 ± 11.8	43.3 ± 11.6

^a*P* < 0.05 *vs* 3 mo after endoluminal gastroplication by Wilcoxon's signed rank test. GSRS: Gastrointestinal symptoms rating scale; SF-36: 36-item short-form.

**Figure 1** Rate of discontinuation or reduction by more than 50% of proton pump inhibitor use.

patients, reducing their PPI dose and improving their QOL. Surgical fundoplication has been shown to be effective in reducing esophageal reflux in erosive GERD, as well as in NERD. Omura *et al*^[16] have reported that, after laparoscopic fundoplication in 21 NERD patients with acid or bilirubin reflux, all subjects experienced improvement in symptoms of heartburn and were able to discontinue or reduce PPI medication. Broeders *et al*^[17] performed Nissen fundoplication in 96 NERD patients and 117 erosive GERD patients, with improvement in symptoms in 89% and 96%, respectively, after 5 years. In addition, there were no differences between the two groups in terms of the effect in reducing PPI medication, improving QOL score, and reducing acid exposure times, suggesting the long-term efficacy of fundoplication. The efficacy of surgical fundoplication thus continues to be established in GERD, as well as in NERD. However,

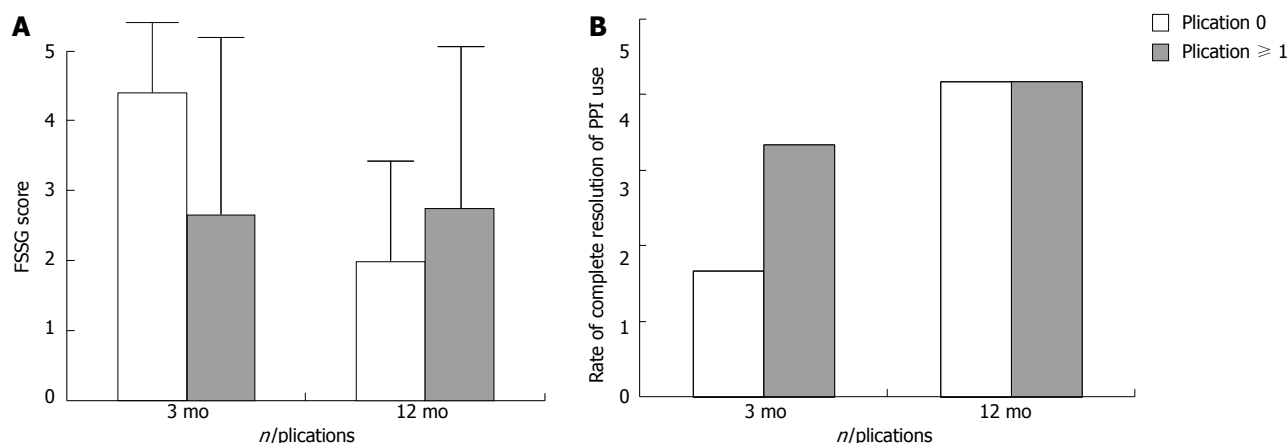


Figure 2 Relationship with the plication number and symptom or proton pump inhibitor use. A: Relationship between the number of plications and the score of the frequency scale for symptoms of gastro-esophageal reflux disease. There is no significant difference between the two groups (remaining plications 0 vs one or more) after 3 or 12 mo after endoluminal gastroplication (ELGP); B: Relationship between the number of plications and the rate of proton pump inhibitor (PPI) use. The group with one or more remaining plications shows a tendency to reduced PPI use 3 mo after ELGP ($P = 0.07$). However, there is no significant difference between the groups after 12 mo of ELGP.

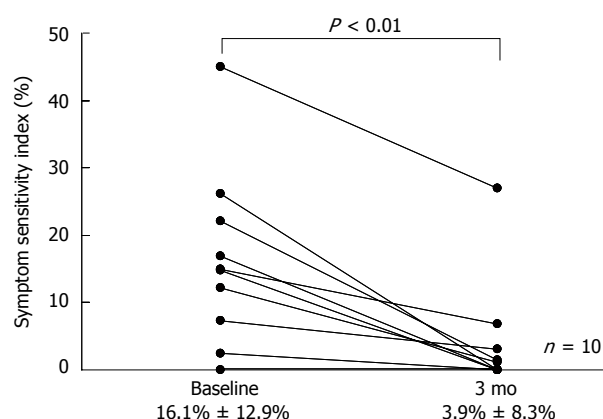


Figure 3 Symptom sensitivity index transition at baseline and 3 mo after endoluminal gastroplication.

it has been reported that surgical fundoplication is associated with complications approximately 10% of the time, and that dysphagia lasting 3 mo or longer has been observed^[28]. The procedure is also associated with an operative mortality of about 0.5% to 0.7%^[29], which may be considered a problem for the treatment of a benign disease. There are also no differences in the long-term (140 mo) effect compared to drug treatment^[30], and the cost is higher compared to 10 years of treatment with omeprazole^[31]. It was in light of this background that endoscopic treatments were proposed as less invasive but effective treatment methods^[32,33]. Endoscopic fundoplication is an extremely safe method among such treatments, and its efficacy in erosive GERD is also being studied^[34,35].

The results of 6, 12, and 24 mo of observation have been reported by Filipi *et al.*^[36], Mahmood *et al.*^[25], and Chen *et al.*^[26] in typical clinical studies of ELGP. All reported significant improvements in heartburn and reflux scores, as well as a significant reduction in PPI medication, and these effects lasted as long as 24 mo. In the only randomized, double-blind, comparative study, which was

conducted by Schwartz *et al.*^[37] in 2007, 60 patients with GERD were assigned to an EndoCinch group, a sham treatment group, and an observation group, each composed of 20 subjects, and the subjects were assessed at 3, 6, and 12 mo. After 3 mo, the active treatment group showed a significant reduction in medication and improvement in GERD symptoms and QOL compared to the sham treatment group, and these effects lasted as long as 12 mo. However, there was no difference in esophageal acid exposure between the treated and sham groups, and 29% of the cases required re-treatment. In the only report of a clinical study in Japan, 48 patients with erosive GERD underwent ELGP and were followed-up for 2 years. On 24-h pH monitoring, there was improvement in the percent time pH < 4 from 23.3% ± 26.3% to 10.4% ± 9.6%, as well as 80% improvement from a Los Angeles endoscopic classification of Grade A, B, or C to Grade O. Overall, 66% discontinued PPIs or H₂RA medication, 76% discontinued at least 50% of their medications, and 54% to 66% experienced complete resolution of GERD symptoms^[15]. Meanwhile, Arts *et al.*^[27] performed ELGP in 20 PPI-resistant GERD patients, and reported that 13 and 6 patients were able to discontinue PPI medication 3 and 12 mo later, respectively, and pH monitoring also revealed normalization. These results showed that this treatment method could be indicated for PPI-resistant patients, but there have thus far not been any reports involving PPI-resistant NERD patients.

As previously reported, the mechanism of ELGP is believed to involve a decrease in esophageal acid exposure^[15]. However, in the present study, 24-h intraesophageal pH monitoring revealed mild worsening rather than improvement in the percent time pH < 4 after ELGP. Although it can be said that this was caused by the fact that pH was monitored prior to ELGP while the patients were on full-dose PPI, the fact that symptoms improved and that the rate of PPI medication decreased in patients with GERD symptoms despite being on PPI medication

suggests that factors other than esophageal acid exposure are involved in the development of symptoms in PPI-resistant NERD patients. ELGP involves the endoscopic formation of folds, which are believed to physically prevent reflux through bosselation at the gastroesophageal junction. However, 24-h intraesophageal pH impedance monitoring in the present study did not reveal significant decreases in the percent time pH < 4 or number of episodes of reflux before and after ELGP. Although the possibility cannot be ruled out that esophageal reflux was not adequately controlled because of the spontaneous sloughing off of plications 3 mo after ELGP, it has also been reported elsewhere that pH monitoring revealed no changes before and after surgery^[36,37], and many questions remain regarding the relationship between esophageal acid exposure and the development of symptoms.

In the present study, the number of symptom events and SSI decreased significantly, regardless of the lack of change in the number of episodes of reflux and SI (Figure 3). These results mean that the specificity of a NERD patient's reflux symptoms did not change, but the subject's sensitivity for reflux decreased after surgery. This suggests that factors other than esophageal reflux are involved in the development of the symptoms of NERD, and the presence of esophageal hyperesthesia may be one such factor. Patients with GERD experience proximal esophageal reflux more than normal individuals, but the incidence of proximal esophageal symptoms is significantly higher in NERD patients than in GERD patients^[38]. In addition, the time for symptoms to develop during 10 min of intraesophageal hydrochloric acid infusion, the intensity of symptoms, and the sensitivity index are significantly higher in NERD patients than in normal individuals, patients with reflux esophagitis, and patients with Barrett's esophagus^[39].

Animal studies have confirmed fibrosis near plications and local thickening of smooth muscle of the gastroesophageal junction^[40,41]. It has thus been postulated that sensory nerves densely distributed in the gastroesophageal junction might be damaged by plication, resulting in a loss of sensitivity^[42]. The lack of apparent differences in symptom scores between cases in which plications completely disappeared and cases in which they remained suggests the involvement of esophageal hyperesthesia in the pathology of PPI-resistant NERD. Mechanisms in which tissue degeneration and scar formation in the gastroesophageal junction result in changes in compliance and internal pressure, as well as transient lower esophageal sphincter relaxation, have also been considered^[43].

GSRS has found overlap in various gastrointestinal symptoms and decreases in the scores of all items in the SF-36, and decreases in health-related quality of life (HR-QOL) have been confirmed in PPI-refractory NERD patients. In the present study, ELGP was found to improve HR-QOL in PPI-resistant NERD patients, and the long-term effects were confirmed not only at 3 mo after surgery, but also at 12 mo, showing no recurrence of GERD symptoms and a decrease in PPI use. These find-

ings suggest that HR-QOL was maintained.

Montgomery *et al.*^[44] conducted a randomized, comparative study of ELGP and placebo treatment in 46 patients with erosive GERD. After 3 mo, there was significant improvement in heartburn symptoms and PPI use in the ELGP group, but it was reported that the differences from the sham treatment group disappeared after 12 mo. Overall, 71% and 67% of the plications remained after 3 and 12 mo, respectively, and the attenuation of the effects was attributed to the decrease over time in the percentage of remaining plications^[45,46]. On the other hand, while an apparent loss of plications over time was observed in the present study of PPI-resistant NERD patients, there was virtually no recurrence of symptoms, and patients were able to wean themselves off of medication over the long term. It is therefore possible that ELGP is more useful in NERD, particularly PPI-resistant NERD that is not amenable to oral treatment, than in erosive GERD. The results also suggest differences in the pathology of erosive GERD and NERD.

Most endoscopic treatment in GERD to date has been in patients for whom oral treatment was effective, but the present study was unique in that it looked at cases not amenable to oral treatment and demonstrated the efficacy and safety of the treatment. However, the study suffered from several shortcomings. The first is the lack of any placebo treatment as a control, and the limited number of cases. In actuality, no sham groups were established in many preceding studies of endoscopic treatment^[15,25-27,36,47]. It is often difficult to establish a rigorous model, because the frequent development of complications in active treatment groups hinders blinding, and because increased efficacy is also sometimes observed in sham groups. In the future, it will be necessary to conduct a blinded, randomized, comparative study with a sufficient sample size in order to confirm the efficacy of ELGP treatment in PPI-resistant NERD patients suggested in this study. Second, the 12-mo observation period was inadequate, and it will be necessary to study efficacy for a longer period of time from medical and economic perspectives. It is also possible that the improvement in symptoms by ELGP in PPI-resistant NERD patients results from a variety of mechanisms, including esophageal hyperesthesia, in addition to the physical action of preventing reflux, and further study from that perspective is also necessary.

Despite the many limitations of this study, this is the first report to show endoscopic treatment to be highly effective and safe in PPI-resistant NERD patients who are not amenable to oral treatment and who suffer from significantly compromised QOL. With the accumulation of evidence in the future, it is possible that there will be new indications for endoscopic therapy, including post-gastrectomy GERD and complementary therapy until surgery or postoperative salvage for GERD.

In conclusion, in this study, ELGP significantly improved subjective symptoms and reduced long-term oral medication in Japanese PPI-resistant NERD patients, and it appears to be a safe and useful method of treatment.

COMMENTS

Background

Non-erosive reflux disease (NERD) refers to a syndrome that is characterized by complaints of reflux symptoms such as heartburn without endoscopic evidence of mucosal injury. The severity and frequency of NERD symptoms is similar to erosive gastroesophageal reflux disease (GERD) and is often not amenable to treatment with oral medication. Especially, PPI-resistant NERD is the most intractable NERD patients. Instead of medication therapy, the surgical treatment of erosive GERD, laparoscopic fundoplication, has been developed. On the other hand endoscopic techniques have been developed recently as less invasive but effective methods for erosive GERD.

Research frontiers

Endoscopic treatments were proposed as less invasive but effective treatment methods for GERD. Especially, endoluminal gastroplication (ELGP) is an extremely safe method among such treatments and its efficacy in erosive GERD is also being studied. Most endoscopic treatment in GERD to date has been in patients for whom oral treatment was effective, but the present study was unique in that it looked at cases not amenable to oral treatment and demonstrated the efficacy and safety of the treatment.

Innovations and breakthroughs

Before and after ELGP, patients' symptoms, quality of life (QOL) and 24-h intra-esophageal pH/impedance (MII-pH) monitoring were assessed. After ELGP, the symptoms, QOL and esophageal sensitivity improved significantly. Furthermore, 66.7% patients were able to discontinue proton pump inhibitor (PPI) medication. This is the first report to show endoscopic treatment to be highly effective and safe in PPI-resistant NERD patients who are not amenable to oral treatment and who suffer from significantly compromised QOL.

Applications

With the accumulation of evidence in the future, it is possible that there will be new indications for endoscopic therapy, including postgastrectomy GERD and complementary therapy until surgery or postoperative salvage for GERD.

Terminology

NERD: It is a syndrome that is characterized by complaints of reflux symptoms such as heartburn without endoscopic evidence of mucosal injury; ELGP is a recently introduced endoscopic therapy for GERD refractory to medical therapy. This novel approach involves the insertion of an endoscopic suturing device into the esophagus to create partial-thickness, internal gastric plications that serve as an anti-reflux barrier.

Peer review

This is a good clinical study in which authors analyze the endoscopic therapy effects for PPI-resistant NERD patients who are not amenable to oral treatment. The results are interesting and suggest that this endoscopic technique create a new indication for NERD therapy, especially PPI-resistant NERD who are the most intractable of NERD patients.

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