Title: Subjective and objective data on esophageal manometry and impedance pH monitoring 1 year after endoscopic full-thickness plication for the treatment of GERD by using multiple plication implants

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Background: Subjective and especially objective data after endoluminal full-thickness gastroplication are scarce.

Objective: To evaluate symptoms and reflux activity 12 months after gastroplication by using multichannel intraluminal impedance monitoring.

Design: Open-label, prospective, single-center study.

Setting: Tertiary referral hospital in Zell am See, Austria.

Patients: Subjects without hiatal hernias with documented GERD and persistent or recurrent symptoms despite treatment with a proton pump inhibitor.

Interventions: A total of 36 patients underwent endoscopic full-thickness gastroplication with 1 or more Plicator implants.

Main Outcome Measurements: Mean Gastrointestinal Quality of Life Index and reflux-specific symptom scores significantly improved on follow-up (P < .01). Atypical reflux, gas/bloating, and bowel dysfunction–specific symptom scores as well as belching and dysphagia scores improved. Twenty-two patients returned for esophageal manometry and multichannel intraluminal impedance testing 1 year after surgery. DeMeester scores decreased from 20 to 10 (P < .029). The median numbers of total, acid, proximal, upright, and recumbent reflux episodes were all significantly reduced (P < .05). Manometric data were virtually unchanged. The percentage of patients taking proton pump inhibitors on daily basis after the procedure was 11.5%. There was only 1 postprocedure incident (bleeding) that required intervention. Three of 36 patients (8.3%) were considered treatment failures because of persistent symptoms and were assigned to undergo laparoscopic fundoplication.

Limitations: No randomized comparison with a sham procedure or laparoscopic fundoplication; follow-up interval.

Conclusions: Endoscopic plication is safe and improves objective and subjective parameters at 1-year follow-up, without side effects seen after laparoscopic fundoplication. Further studies on the clinical merit of this procedure in specific patient populations are warranted. (Clinical Trial registration number: NCT01453985.)

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GERD is a common disorder of the alimentary tract, with a prevalence of 10% to 20% in Western countries.1 Most patients with typical reflux symptoms are sufficiently treated by acid-suppressive medical therapy, but although esophagitis heals in virtually all patients, as many as 40% still have symptoms.2,3 Patients whose symptoms are as-

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sociated with reflux but are not adequately responding to acid suppressive therapy can be identified by combined multichannel impedance pH monitoring and are candidates for laparoscopic antireflux surgery (LARS). Long-term follow-up has demonstrated a good to excellent outcome in most patients after LARS. However, potential benefits of surgery must be weighed against potential side effects. These include epigastric pain, gas/bloating (ability to belch or fullness), and bowel dysfunction (obstipation, flatulence, and diarrhea). Patients undergoing LARS are expected to accept a trade-off between relief of GERD symptoms and the potential side effects after the procedure. An approach to the treatment of GERD that obviates the need for antireflux medication and improves symptoms and quality of life (QoL) without side effects seen after LARS would be desirable.

As an alternative to acid-suppressive medications and LARS, a number of flexible endoscopic techniques have been developed and evaluated. The procedures were primarily designed to be used in patients with relatively normal anatomy of the esophagogastric junction (small or no hiatal hernia). Most of the techniques have been abandoned because of poor effectiveness, durability, and safety concerns. Endoscopic full-thickness plication has shown even long-term efficacy regarding QoL, symptom scores, and reduction of proton pump inhibitor (PPI) use in prospective multicenter trials. However, plication and other endoscopic procedures have been criticized for normalizing esophageal acid exposure in only 30% to 40% of the patients treated. Esophageal 24-hour pH normalization is widely considered a crucial component of GERD treatment because one of the goals is to avoid long-term complications.

This single-center study evaluates the outcome of patients 1 year after endoscopic full-thickness plication. The article reports 1-year results, including subjective patient data (well-being, symptom scores, medication use, side effects) and objective measurement parameters of esophageal manometry and 24-hour esophageal impedance pH monitoring.

**PATIENTS AND METHODS**

From October 2007 to October 2010, a total of 420 individuals were assessed for eligibility at the Department of General Surgery, Public Hospital of Zell am See, by a diagnostic program. The patients underwent a series of diagnostic studies, including gastroscopy, barium esophagography, esophageal manometry, and esophageal multichannel intraluminal impedance testing. Patient inclusion criteria were at least 1 typical reflux symptom despite treatment with a PPI for at least 6 months and pathologic esophageal acid exposure as documented by a reflux-related DeMeester score of 14.7 or higher or symptom correlation of 50% or greater, or more than 73 reflux episodes.

**Take-home Message**

- Endoscopic full-thickness plication is a safe and well-tolerated procedure that significantly improves quality of life and eliminates GERD symptoms, without the side effects seen after laparoscopic fundoplication.
- Longer follow-up of its effect on reflux control is essential. Further studies aiming at identifying those patient groups who will benefit from this endoscopic treatment modality are warranted.

Patient exclusion criteria were younger than 18 years, American Society of Anesthesiologists physical status classification higher than II, evidence of hiatal hernia measuring more than 2 cm, paraesophageal hernia, previous esophageal or gastric surgery, and pregnancy.

Forty patients fulfilled study inclusion criteria; of these, 36 patients were assigned to and received treatment with endoscopic full-thickness plication. Informed consent for participation in the study was obtained from all patients. All procedures were performed by the same surgical team. Study approval was obtained from the institution’s ethics committee.

**Endoscopic plication technique**

All procedures were performed with the patients under general anesthesia. No preprocedure antibiotics were given. A standard upper endoscopy was performed and a Savary guidewire was placed on gastroscopy withdrawal. The Plicator (Ethicon Endosurgery, Sommerville, NJ) was introduced over the guidewire and into the stomach. A 5.8-mm video endoscope was passed through the Plicator, and the Plicator’s distal end was retroflexed to the anterior gastric cardia approximately 1 cm below the GE junction under direct endoscopic visualization. The Plicator arms were opened, and the endoscopic tissue retractor was advanced deeply into the gastric cardia. The tissue retractor was then drawn back to gather tissue between the open arms of the Plicator. The arms were closed and a pretied transmural pledgeted suture was deployed. The Plicator and the gastroscope were removed, and the gastroscope was reinserted to evaluate the resulting plication. If necessary for a tight closure of the restructured gastroesophageal junction, 1 or 2 additional sutures were placed in the same manner, as described previously, until a tight closure around a 5.8-mm video endoscope was achieved. In this protocol, additional treatment with another suture was permitted and performed in the same manner in case of inadequate response to therapy.

**Esophageal manometry**

All patients were studied while in the supine position and after an overnight fast. Manometry was performed using a conventional 4.5-mm nasoesophageal 8-lumen
polyethylene catheter, continuously water perfused (0.5 mL/min) by a low-compliance pneumohydraulic capillary infusion pump system. Five of the 8 channels with exit ports located at 5-cm intervals along its length and oriented radially around the circumference of the catheter were linked to a transducer; the pressures were recorded on a computerized polygraph and analyzed on a personal computer.14,15

The lower esophageal sphincter (LES) resting pressure, overall length, and abdominal length were obtained as arithmetic mean values from each of the 5 radial side holes during a standard station pull-through. The LES resting pressure was measured as the mid-respiratory resting pressure (mm Hg) in the high-pressure-zone, using mid-respiratory gastric pressure as zero reference. The transdiaphragm pressure gradient was measured as the mean mid-respiratory intra-abdominal pressure difference to mid-respiratory intrathoracic pressure from each of the 5 radial side holes. Esophageal body motor function was assessed by recording pressures from side holes located at 3, 8, 13, 18, and 23 cm above the upper margin of the LES during 10 wet swallows (5 mL each) at 20- to 30-second intervals. The esophageal amplitude was calculated from the mean intrasophageal baseline to the peak of the wave and presented in milligrams of mercury (mm Hg). Each wave was classified as normal, hypotensive (<30 mm in 1 of the 2 distal channels) or defective (interrupted or dropped, ie, <15 mm in 1 of the 2 distal channels, or simultaneous over a 5-cm segment, ie, beginning within 0.25 seconds within each other). Motor function was then assigned to 4 quality groups as a result for every motility analysis: group 1, perfectly normal, more than 80% normal waves; group 2, normal, more than 50% normal waves; group 3, slightly disturbed, more than 50% normal or hypotensive waves; group 4, heavily disturbed, less than 50% normal or hypotensive waves.

24-hour ambulatory esophageal impedance pH monitoring

All patients had discontinued antisecretory therapy at least 1 week before and were encouraged to maintain their normal activities and meal times and to remain upright during the day with 1 short nap allowed. We used an ambulatory Sleuth multichannel intraluminal impedance (MII) pH monitoring system (Sandhill Scientific, Highland Ranch, Col). A 2.1-mm nasogastric probe was inserted with 2 antimony pH electrodes located 5 cm above the manometrically located lesions and 15 cm more distal and 8 impedance electrodes, allowing measurement of the intraluminal impedance in 6 segments at 3, 5, 7, 9, 15, and 17 cm above the LES. Data were recorded on a flash card of the portable datalogger at 50 samples per second. Patients were asked to report meal times, posture changes, and symptoms by pressing 1 of 3 different event buttons on the data recorder. Reportable symptoms were heartburn, regurgitation, cough, or others, if troublesome for the patient. Meal times were excluded from the analysis. The recorded tracings were preanalyzed on a PC by an auto-scan algorithm (Bioview Analysis) and visually revised by an expert reader at 3-minute intervals. Further technical details were published previously.16

We used the Symptom Index (SI), the number of symptoms associated with reflux events based on a 5-minute time window divided by the total number of symptoms. The SI was deemed positive if it was more than 50%.17 GERD was diagnosed if the total number of reflux events in 24 hours exceeded 73,18,19 when the reflux-related composite pH score according to DeMeester exceeded 14.7, or if the SI was positive for symptoms reported at least 3 times.

Symptom and side effect evaluation

Symptom and postoperative side effect evaluation was carried out in a standardized way using a written questionnaire assessing the severity and intensity of 14 symptoms on a 4-point scale.13 In particular, the symptoms of heartburn, regurgitation, chest pain, cough, hoarseness, asthma, dysphagia, fullness, diarrhea, flatulence, constipation, belching, bloating, and distortion of taste were graded as none (0), once per week (1), several times per week (2), daily (3), and constantly (4). The intensity of the above symptoms was graded as none (0), mild (1), moderate (2), severe (3), and extremely severe (4). To obtain the ultimate result, the frequency of each symptom is multiplied by its degree, resulting in scores from 0 to 16 for each symptom. Higher scores indicate more severe symptoms. Additionally 4 different scores were extracted to assess symptoms specific for reflux (heartburn, regurgitation, chest pain), gas/bloating (fullness), bowel dysfunction (diarrhea, constipation, flatulence), and atypical reflux symptoms (cough, hoarseness, asthma, distortion of taste).

QoL and antireflux medication evaluation

QoL was evaluated by means of the Gastrointestinal Quality of Life Index (GIQLI).20 This questionnaire is well established and has been validated and recommended by the European Study Group for Antireflux Surgery.21 Including 36 items, the general responses to the GIQLI are graded from 0 to 144 points. The mean value in the normal population is 122.6. The GIQLI is divided into 5 subdimensions: GI symptoms (0-76 points), emotional status (0-20 points), physical functioning (0-28 points), social functioning (0-16 points), and a single item for stress of medical treatment (0-4 points). Higher scores indicate a better QoL. Additionally, patients were asked for regular daily or on-demand use of acid-blocking medication.

Follow-up

Follow-up was performed 1 year after surgery. Follow-up studies included esophageal manometry and impedance pH monitoring. Evaluation of QoL, symptoms, and medication use was done at baseline and on follow-up by questionnaires.
that were administered to all patients by an independent observer. Seven days of cessation of antireflux medication preceded the follow-up evaluation of study participants.

Statistical analysis
Statistical analysis was performed by using SPSS Statistical Analysis Software (SPSS Inc, Chicago, Ill). All datasets were tested for normal distribution by the Kolmogorov-Smirnov test. Except for the numbers of preinterventional proximal reflux episodes and postinterventional recumbent reflux episodes, they were normally distributed. All data were presented as median, 25th to 75th percentile range and 95th percentile. If normally distributed, they were additionally presented as mean and standard deviation. Comparison of pre- and postprocedural data was done by using a paired t test or Wilcoxon signed rank test on a per-subject basis. \( P < .05 \) was regarded as significant change.

RESULTS

There were 9 female and 27 male patients with an age of \( 46.5 \pm 12.8 \) years, and a mean body mass index of \( 26.28 \pm 3.52 \) kg/m\(^2\) before the procedure. After the procedure, the body mass index increased to \( 27.18 \pm 3.49 \) kg/m\(^2\), but not significantly. Endoscopically distinct mucosal breaks in the lower esophagus were found in 4 patients. Of the 36 patients, 1 received a single Plicator implant, 20 received 2, 14 received 3 Plicator implants, and in another patient, 4 Plicator implants were primarily deployed. The mean general GIQLI was \( 93.77 \pm 22.01 \) points, thus significantly impaired (\( P < .01 \)) compared with healthy individuals (122.6 \pm 8.5 points). All patients were taking PPI or had been on standard dose of a PPI for at least 6 months and were dissatisfied because of persistent or recurrent symptoms despite taking the medication.

Postprocedural gastric bleeding from the plication site developed in 1 female patient requiring transfusions and was easily controlled endoscopically. Other than that adverse event, no other adverse events requiring intervention were observed. Seven of the 36 patients returned to the hospital before their scheduled 12-month follow-up visit because of persistent symptoms. One of these patients elected to undergo LARS and was lost to follow-up. The other 6 patients elected to receive another plication implant. Four of these patients were followed for 1 year after the procedure. The other 2 patients returned to our hospital about 6 weeks after the procedure because of persistent symptoms and underwent LARS and were lost to follow-up. In total, 3 of 36 patients (8.3%) underwent LARS before their 1-year follow-up and were considered as failures; the operations could be completed laparoscopically with no intraoperative complications. During operation, a large esophageal hiatus was found in all patients and was considered the reasons for failure.

Twenty-six of 36 (72.2%) patients were available for the 1-year follow-up after plication (mean follow up time was \( 14.2 \) weeks). Twenty-two patients (61.1%) returned for esophageal manometry and MII testing 1 year after surgery. Twenty-six patients completed the symptom checklist and GIQLI questionnaire; 3 of these patients agreed to complete the questionnaires sent to them via mail.

Three patients underwent LARS within the 1-year period and were therefore lost to follow-up; the other patients refused to participate further in the study because of long-distance constraints.

QoL and antireflux medication use on follow-up

One year after the procedure, QoL had significantly improved from \( 93.77 \) points to \( 116.5 \) points (\( P < .01 \) (Table 1).

Before plication, all patients stated that they were taking a PPI or had been taking a standard dose of a PPI for at least 6 months and were dissatisfied because of persistent or recurrent symptoms despite treatment. On follow-up, 10 of 26 patients (38.5%) stated that they took a PPI as needed, 3 of 26 (11.5%) stated that they were taking a PPI on a daily basis, and 13 of 26 (50%) stated that they did not take a PPI.

Symptoms and side effects

Reflux-specific symptom scores were highly significantly reduced on follow-up (\( P < .01 \)). Atypical reflux-, gas/bloating-, and bowel dysfunction–specific symptom scores improved, but not significantly. In addition to belching and dysphagia scores. The mean belching score decreased from \( 5.24 \pm 4.13 \) to \( 3.41 \pm 2.76 \) (\( P < .122 \)), and the dysphagia score decreased from \( 1.57 \pm 2.49 \) to \( 0.68 \pm 2.08 \) (\( P < .292 \) (Table 2, Fig. 1).
24-hour multichannel impedance pH monitoring data and esophageal manometry data

The mean numbers of total, acid, proximal, recumbent, and upright reflux episodes were all highly significantly reduced after the procedure. The mean number of recumbent reflux episodes was significantly reduced at 12-month follow-up. Nonacid reflux episodes decreased, showing a clear tendency, but not reaching significance ($P < 0.059$) (Table 3).

Mean composite pH score according to DeMeester was significantly reduced at 12-month follow-up (Table 4).

Manometric data were virtually unchanged. The mean LES resting pressures were 11.76 mm Hg at baseline and 12.12 mm Hg at follow-up. The procedure had no significant influence on the esophageal body motility, and the preoperative esophageal motor function had no influence on the outcome.

DISCUSSION

Several endoscopic therapies for GERD emerged during the past decade. Although some of these techniques have fallen out of favor, others have been withdrawn from the market because of safety issues. Endoscopic full-thickness plication is under continuing evaluation and has proved to be safe, reduces GERD symptoms and medication use, and improves QoL scores. This study underlines results of previous reports that demonstrated the therapeutic effect of endoscopic plication. Furthermore, it shows that side effects are minimal, whereas symptoms such as gas/bloating, dysphagia,
and bowel dysfunction show some degree of improvement. This fact is very important considering that there is a subgroup of individuals with mild symptoms who are not willing to undergo surgery because of the mentioned side effects, but seek an effective, minimally invasive therapy. From the patient’s point of view, the so-called heuristic endpoints, such as symptom resolution, duration of convalescence, patient satisfaction, well-being, and QoL, are at least as important as the classic outcomes. Although endoscopic full-thickness gastroplication has proved to provide subjective satisfaction with the treatment, it has been criticized, like other endoscopic procedures, for not normalizing esophageal acid, which is widely considered as a crucial component of GERD treatment. In this study, an MII pH monitoring system was used to assess objective data. The data of this study clearly demonstrate that symptom improvement does not apply to the placebo effect, as documented by the results of MII monitoring. Furthermore, previously reported MII findings by von Renteln et al, who evaluated gastroplication outcomes 6 months after procedure are confirmed here.

The study demonstrates a significant reduction of DeMeester scores and of total, acid, proximal, upright, and recumbent reflux episodes, despite unchanged LES parameters. Both the diaphragm and the LES contribute to gastroesophageal sphincter competence. Gastroplication does not alter the esophageal hiatus. This could explain why the LES parameters are unchanged after the procedure. The antireflux mechanism of gastroplication does not seem to depend on sphincter pressure augmentation but most likely on a decrease intransient sphincter relaxations and reconstruction of the gastroesophageal valve.

Although half of all the patients were not dependent on antacid medication, the other half was taking a medication at follow-up (11.5% daily, 38.5% as needed), and 8.3% of patients were assigned to undergo laparoscopic fundoplication because of persistent symptoms. All of the operations could be completed laparoscopically with no intraoperative complications, and the patients are currently symptom free. During the operation in every case, a large esophageal hiatus was found and was considered to be the cause of failure because it is well known that the anatomic configuration of the diaphragm’s esophageal hiatus plays a role in the pathophysiology of GERD. We assume that even if only a small hiatal hernia is demonstrated before surgery, a large hiatal defect influencing postoperative outcome is possible. Although large hiatal hernias are easily identified in radiological and endoscopic

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studies, the diagnosis of a small hiatal hernia is rather difficult. The current endoscopic practice of diagnosing a hiatal hernia and measuring its size by using the centimeter markings on the endoscope is inaccurate. A different approach to endoscopically grade a hiatal hernia is to assess the appearance of the esophagogastric junction from a retroflexed position. The progression from normal anatomy to a type I hernia was well illustrated in an analysis of flap valve integrity as a predictor of reflux symptoms. Hill grades 1-4; grade 1, normal closed valve; grade 4, open valve, associated hiatal hernia. The classification leading to better outcomes. Recently, Khajanchee et al demonstrated that patient selection by body mass index, DeMeester score, and symptom intensity significantly improves the outcome after gastroplication.

Nevertheless, the results of this study should be approached with caution because of inherent limitations. First, the follow-up period was short because the aim of the study was to validate the positive therapeutic results of this modality with subjective functional data and thereby to preclude bias introduced by the placebo effect. Longer term data are, however, needed for further evaluation of the treatment effect. Second, the study population is limited; therefore, a type II statistical error cannot be ruled out. Third, comparison with either a sham procedure or a laparoscopic antireflux procedure was not undertaken. Nevertheless, a quasi-randomized study recently published by our study group addressed this issue, suggesting a higher degree of improvement for the operative group at the expense of higher dysphagia rates.

In conclusion, this study demonstrates that endoscopic full-thickness plication is a safe and well-tolerated procedure that significantly improves QoL and eliminates GERD symptoms, without the side effects seen after laparoscopic fundoplication. Furthermore, midterm objective data clearly demonstrate that subjectively satisfied patients are not placebo responders. The majority of patients can expect that the use of a PPI after gastroplication will be reduced and their symptoms will improve. Thus, endoscopic plication could possibly be an adjunctive therapy for patients dissatisfied with PPI therapy. Furthermore, surgical treatment remains an option in case the endoscopic treatment fails to control reflux symptoms. Although endoscopic plication seems an attractive, minimally invasive alternative in the treatment of GERD, longer follow-up of its effect on reflux control is essential. Further studies aiming at identifying those patient groups that will benefit from this endoscopic treatment modality are warranted.

REFERENCES


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