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A One-Year Follow-up Study of Endoluminal Gastroplication (Endocinch) in GERD Patients Refractory to Proton Pump Inhibitor Therapy

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In a subset of patients with gastroesophageal reflux disease (GERD), symptoms persist in spite of proton pump inhibitor (PPI) therapy. Endoscopic gastroplication (EG) was reported to provide a novel therapeutic option in GERD. To evaluate symptomatic and objective outcome of EG in PPI refractory GERD, consecutive GERD patients with persisting reflux symptoms during at least 2 months double dose PPI were recruited for EG (Endocinch). Exclusion criteria were high-grade esophagitis, Barrett's esophagus, and hiatal hernia >3 cm. Symptoms and PPI use were evaluated before and 1, 3, and 12 months after the EG; 24-hr pH monitoring off PPI was performed before and after 3 and 12 months. All data are given as mean ± SD and were analyzed by Student's *t* test. Twenty patients (10 females; mean age, 45 ± 11 years) were recruited. Under conscious sedation with midazolam (6 ± 2 mg) and pethidine (53 ± 5 mg), a mean of 2.0 ± 0.2 sutures was applied during a procedure time of 33 ± 6 min. Throat ache and mild epigastric pain for up to 3 days after the procedure were the only adverse events. At 3 and 12 months symptom score (11.6 ± 6 vs. 6.4 ± 3.7 [$P < 0.01$] and 7.1 ± 4.5 [$P < 0.05$]) as well as pH monitoring (% time pH < 4: 17.0 ± 11.1 vs. 8.1 ± 5.7% [$P < 0.01$] and 9.8 ± 4.1% [$P < 0.01$]) significantly improved. Ph monitoring was normalized (<4% of time) in seven patients after 3 months. PPIs could be stopped in 13 patients, with 2 patients still using H_2-blockers and 1 using cisapride after 3 months. After 12 months only six patients were free of PPI use and pH monitoring was normalized in six patients. We conclude that EG provides short- and medium-term symptomatic and objective relief to a subset of GERD patients refractory to high-dose PPI.

KEY WORDS: endoluminal gastroplication; proton pump inhibitor; gastroesophageal reflux disease; pH monitoring.

Gastroesophageal reflux disease (GERD) is one of the most frequent gastroenterological problems in Western countries. Surveys revealed that up to 44% of adults experience heartburn at least once a month and daily symptoms occur in almost 10% of the Western population (1, 2). GERD not only is associated with symptoms, but also may cause complications like strictures, Barrett's esophagus, and adenocarcinoma of the esophagus (3).

Medications interfering with acid production, especially proton pump inhibitors (PPIs), are the cornerstone of GERD treatment. The efficacy of PPIs is well established, with up to 90% of patients with reflux disease becoming asymptomatic while taking PPIs (4). A challenging problem remains the treatment of those patients with proven GERD who have only a small or partial response response to high doses of PPIs (5). For most of these patients, a fundoplication can be proposed as a more definite and effective treatment modality, especially as the laparoscopic

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approach has increased in acceptance (6, 7). Despite the high success rate of surgery in resolving the typical reflux symptoms, a substantial morbidity and mortality exists. Complications like dysphagia, inability to belch, diarrhea, and gas bloat may develop in up to 30% (6–8). Furthermore, several recent observations tempered the enthusiasm for antireflux surgery. In a retrospective study, Spechler *et al*. found that up to 62% of the patients were still taking antireflux medication 10 years after open fundoplication (9). Moreover, in that study no long-term differences were found in the severity of reflux, reflux score, and overall satisfaction between medically and surgically treated patients. An analysis of the outcome patients who had undergone laparoscopic fundoplication in a managed care organization confirmed that a high proportion of these patients reported new symptoms after the surgery and up to one-third remained on antisecretory drugs (10). Finally, antireflux surgery is considerably less successful in patients with a poor response to medical therapy (11, 12).

During the last few years, endoscopic procedures aiming at improvement of the barrier function of the lower esophageal sphincter (LES) were proposed. In theory, they could provide an attractive alternative because these procedures do not have the side effects of surgery, they can be performed on an out patient basis without general anesthesia, and patients can stop their maintenance medical treatment (13). One of these techniques, endoscopic gastroplication (EG), uses an endoscopic suturing device developed by Swain and colleagues and commercialized by CR BARD Endoscopic Technologies (Billerica; USA). The basis of the procedure is to construct plications in the gastric mucosa at the level of the esophagogastric junction (14–16). It was shown to provide control of reflux symptoms for up to 1 year after the procedure (16–18) and preliminary data suggest long-term efficacy in certain patients (19).

The aim of the present study was to evaluate the use of EG in the treatment of GERD patients with an insufficient response to high doses of PPIs. We evaluate the influence of EG on symptoms, on esophageal acid exposure, and on the ability to stop medical therapy in GERD patients with an incomplete response to medical therapy.

MATERIALS AND METHODS

A prospective single-center study of 20 GERD patients with an insufficient response to high doses of PPIs was performed after approval of the ethics committee of our hospital. Written and informed consent was obtained from each patient.

Patients. Consecutive GERD patients with established GERD and with partial or no response to high-dose PPI or a combination of PPI with H_2-blockers, cisapride, or baclofen (20) were offered treatment with EG. All patients had proven reflux on pH monitoring, were known to be poorly responsive to medical therapy, and were prepared to undergo clinical follow-up for at least 12 months. Exclusion criteria were age <18, high-grade esophagitis (grades 3 and 4 according to the Savary–Miller classificaition [21]), and Barrett's esophagus. Patients with a large hiatal hernia (>3 cm) were also excluded.

Symptom Evaluation. Symptoms were evaluated before EG without treatment and 1, 3, and 12 months after EG. A previously described reflux score was obtained off medical therapy. The severity of 14 different typical and atypical reflux symptoms (heartburn, acid regurgitation, food regurgitation, chest pain, nausea, vomiting, choking, dysphagia, odynophagia, throat ache, hoarseness, coughing, dyspnea, wheezing) was scored from 0 to 3 (0 = absent, 3 = interfering with daily activity). A cumulative reflux score was obtained by adding all numbers (20).

Ambulatory pH Monitoring. Ambulatory esophageal pH monitoring was performed using an antimony pH electrode with a separate skin reference electrode (Synectics Medical, Stockholm, Sweden). The data were stored on a portable digital recorder (Digitrapper Mk III, Synectics Medical, Stockholm, Sweden). Before each study, the pH probe was calibrated in buffer solutions of pH 7 and 1. An episode of acid reflux was defined as a decrease in esophageal pH to <4 for more than 10 sec (22).

Endoscopic Gastroplasty Procedure. The Bard Endoscopic Suturing System was used to perform EG. All procedures were performed by a team of two endoscopists (JA, JT) and one of two endoscopy nurses. The endoscopists as well as the nurses had extensive training on an animal model prior to the patient procedures. After sedation with midazolam and pethidine, a classical upper gastrointestinal endoscopy was performed and the presence of erosive esophagitis, hiatal hernia, and other lesions was noted. A 12-mm-diameter overtube was positioned at the end of the endoscopic evaluation. Through the overtube a second endoscope, with the Bard capsule attached at the tip, was advanced just below the Z-line. A fold tissue was sucked into the cavity of the sewing capsule and a needle with wire and tag was advanced through the sucked mucosa. The suction was stopped and so the first stitch was completed. A second stitch was placed at the same distance but turned 30° to 45° away from the first. The two stitches were then clipped together and the wires cut using the BARD clip and cut device. We intended to place three plications during each procedure: a first one one 1 cm below the Z-line, a second one just below the Z-line and a third one at the same level with approximately 120° clockwise rotation.

Follow-up Protocol. Twenty-four hour pH monitoring off PPI was performed before and after 3 and 12 months. Drugs interfering with esophageal acid exposure were always stopped at least 7 days before the pH monitoring. An endoscopic evaluation to determine the grade of esophagitis and to count the residual stitches was planned after 3 and 12 months. In the absence of clinical improvement a second procedure, aiming at placing additional sutures, was performed.

Statistical Analysis. Symptom severity scores, use of medication, and esophageal acid exposure before and after the EG were compared using two-tailed Student's t test and chi-square testing. Differences were considered to be significant at the 5% level. All data are given as mean $\pm$ SE.

RESULTS

Patient Characteristics. Twenty patients (10 female) were enrolled. The mean age was 45 ± 11 years and

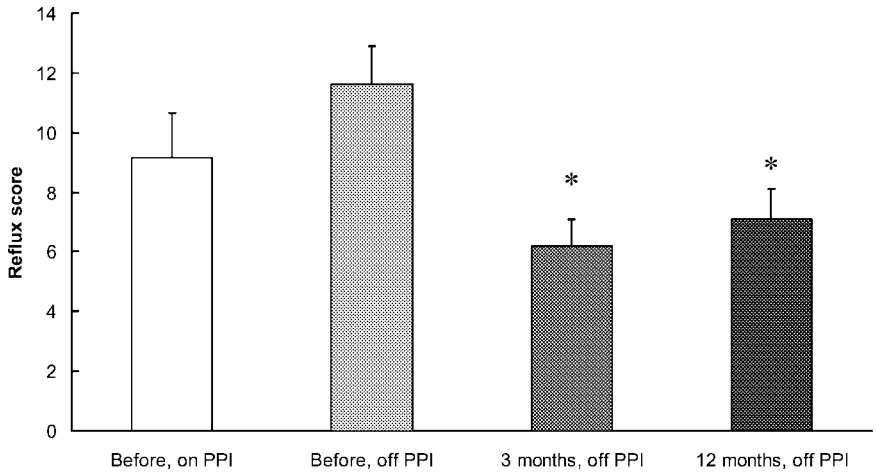

Fig 1. Reflux score before and 3 and 12 months after the Endocinch procedure. $^{*}P < 0.05$ compared to the score off PPI before the procedure.

their mean body weight was 78 ± 11 kg. The average duration of reflux symptoms before the intervention was 5.4 ± 4.3 years. All patients had proven pathological pH monitoring off therapy before they were recruited for EG. In Belgium, endoscopy with grading of esophagitis according to the modified classification of Savary and Miller[36] is the basis for PPI reimbursement. The historical index endoscopy before the start of PPI therapy showed no esophagitis in six patients, grade 1 esophagitis in nine patients, and grade 2 esophagitis in five patients.

Furthermore, all patients had a well-documented history of persistent symptoms or lesions under double-dose PPIs ($n = 15$) or a combination of double-dose PPIs with H_2-blockers ($n = 2$), with cisapride ($n = 1$), or with baclofen ($n = 2$). While receiving these treatments, 12 patients had documented pathological pH monitoring, one patient had pathological duodenogastroesophageal reflux monitoring, and four patients had persisting erosive esophagitis (grade 1 and grade 2 esophagitis each in two patients).

Endoscopic Gastroplasty Procedure. All patients received conscious sedation with a mean of 6 ± 2 mg midazolam and 53 ± 5 mg pethidine. Nine of the 20 patients underwent one procedure, 2 procedures were necessary in 10 patients, and 1 patient, in whom the first procedure failed due to a technical problem with the suturing device, had three interventions. Thus, a total of 32 procedures were performed in 20 patients. The mean procedure time was 33 ± 6 min.

The plications were placed below the Z-line, 1 cm apart, (vertical position), in most patients (15/20). Two horizontal plications were placed in two patients, and a combination of horizontal and vertical position in one patient. Only one plication was created in one patient and no successful plications were obtained in another patient. Failure to place a stitch after mucosa was sucked into the capsule and the needle was advanced occurred in 26% of all attempts.

Symptom Scores. Symptom scores were obtained in all patients before EG and 1, 3, and 12 months afterward. The mean symptom score without treatment was 11.6 ± 1.3, and after 1 and 3 months the scores were 7.2 ± 0.9 ($P < 0.05$) and 6.2 ± 0.9 ($P < 0.01$), respectively. One year after the procedure, reflux scores remained significantly improved (7.1 ± 1.0; $P < 0.05$) (Figure 1). There was no correlation between the number of plications and the change in reflux symptom score. Demographic or symptomatic characteristics did not correlate with the changes in reflux symptom score.

Use of Antisecretory Drugs. After 3 months, 13 patients were able to stop the intake of PPI therapy (65%; $P < 0.001$). One year after the EG only six patients remained asymptomatic without treatment ($P < 0.01$). Another five had a clear subjective improvement under treatment that previously failed to provide relief. After the end of the study, two patients with insufficient subjective improvement were referred for a Nissen fundoplication which was not adversely influenced by the previous EG procedures. At the end of the study, only six patients (30%) had completely stopped PPI intake, and five were now well on PPI doses that previously had failed to provide symptom relief (Figure 2).

Upper Gastrointestinal Endoscopy. After the EG, three of the four patients with an initial erosive esophagitis that persisted under PPI therapy had the same grade of esophagitis at 3 and 12 months. One patient improved from grade 2 to a grade 1 esophagitis after 3 months and complete healing after 12 months.

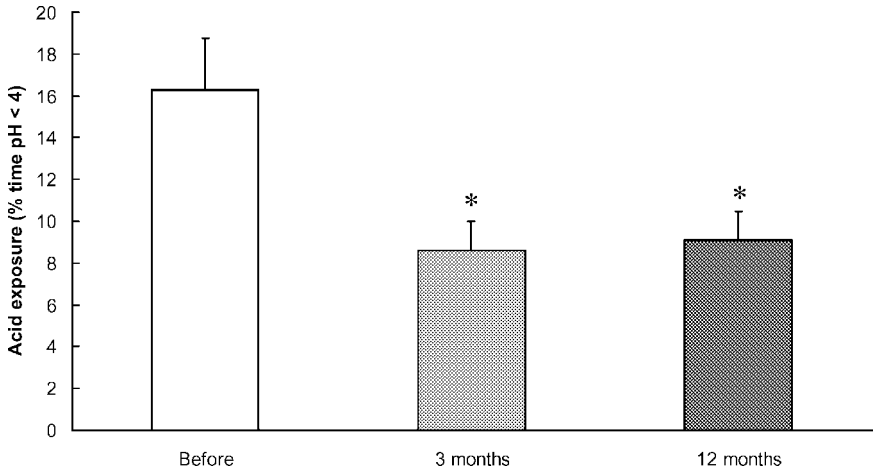

Fig 2. Medical treatment before and 3 and 12 months after the Endocinch procedure. $^{*}P < 0.05$ compared to before the procedure.

Thirteen patients were able to stop PPI intake after 3 months, and this was not accompanied by the occurrence of esophagitis. Although the majority of these patients were documented with erosive esophagitis preceding PPI treatment, no recurrence of esophagitis was seen after EG and interruption of PPI therapy, at either 3- or 12-month evaluation.

Twenty-Four-Hour pH Monitoring. Esophageal pH monitoring was significantly improved after 3 months, with the percentage of time pH <4 decreasing from $17.0 \pm 2.5\%$ before to $8.1 \pm 1.3\%$ after 3 months ($P < 0.01$). In 11 patients, a second EG procedure was performed after initial pH monitoring. This led to a further nonsignificant decrease in acid exposure, from $10.7 \pm 0.9\%$ before to $8.5 \pm 0.7\%$ of the time ($P = 0.1$). After 3 months, pH monitoring was normalized in six patients (30%). After 1 year pH monitoring was still significantly improved: acid exposure was decreased from 17.0 ± 2.5 to $9.1 \pm 1.4\%$ ($P < 0.01$) (Figure 3). After 12 months of follow-up, the same six patients (30%) had a normalized pH monitoring. The Demeester score showed similar improvement (63 ± 9 vs. 32 ± 5 at 3 months and 41 ± 6 at 12 months, $P < 0.01$). There was no correlation between the number of plications and the change in pH monitoring. Demographic and symptomatic characteristics were not related to improvement in pH monitoring.

Adverse Events. Both a mild throat ache and mild epigastric pain were commonly observed immediately after the procedure. The former is most likely related to the use of an overtube and the latter to the placement of the stitches. Both symptoms invariably were mild and always resolved spontaneously in 2 to 3 days.

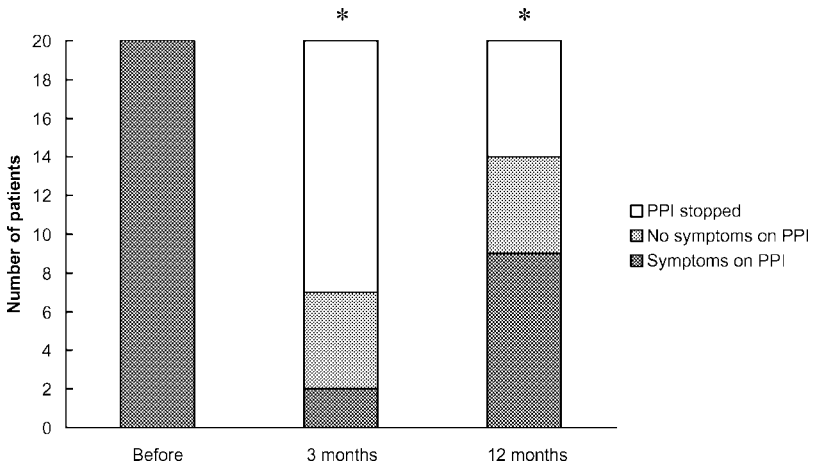

Fig 3. Esophageal pH-monitoring before and 3 and 12 months after the Endocinch procedure. $^{*}P < 0.05$ compared to before the procedure.

One patient developed dysphagia. A repeat endoscopy was performed after 4 days and showed a false lumen created by two folds which were opposed to each other, rather than at a 45° interval. The knot was easily cut using endoscopic scissors and the dysphagia readily disappeared.

DISCUSSION

Medical treatment with PPI remains the gold standard in GERD therapy. However, not all patients are fully asymptomatic under medical therapy and others are not willing to comply with long-term intake of medication. In these patients, laparoscopic antireflux surgery is the main therapeutic alternative.

Recently, a number of endoscopic procedures aimed at treating GERD have been intoruced. These include injection therapies (Enteryx, Gatekeeper), radiofrequency energy delivery (Stretta), and endoscopic gastroplasty (Endocinch, Full-thickness Plicator, Endoscopic Suturing Device) (13). Several studies have assessed the endoscopic gastroplasty in the treatment of GERD (16–19, 23–26). These studies mainly recruited patients who experienced good symptom relief during medical GERD treatment but who wanted to consider a nonmedical treatment option. In general, these studies obtained satisfactory subjective symptom relief, but the objective evaluation of the antireflux effect by means of pH monitoring showed only weak or nonsignificant improvement (16–19).

In clinical practice, patients with persisting reflux symptoms in spite of medical therapy are a particularly difficult group to treat. In these patients, surgery was shown to have a less favorable outcome (11, 12). The aim of the present study was to investigate the therapeutic potential of EG in this setting. Similar to most studies using EG, we observed that the reflux symptom score was significantly improved, after both 3 and 12 months. Similar to the reported experience, no major complications occurred and the most frequently observed side effects were mild and transient throat ache and epigastric pain. One patient developed dysphagia immediately after the procedure, which was resolved by endoscopically cutting one plication where the stitches were opposite each other. This successful intervention confirms the reversibility of the endoscopic gastroplasty procedure.

Unlike most other studies, we obtained a significant improvement in esophageal pH monitoring, with acid exposure decreasing from 17 to 10% after 12 months. This could partly be explained by the higher baseline acid exposure values in the present study, which recruited refractory patients, compared to the studies that have been reported so far (16–19, 23–26). A second important factor contributing to the improved pH-metry result might be the study protocol's provision of additional sutures whenever the initial response was insufficient. This is an acceptable approach, as the procedure is done on an outpatient basis under conscious sedation, has only minimal complications, and the patient's original EG set can be reused.

Also similarly to most studies, PPI therapy was stopped in 13 of 20 patients after 3 months (16–19, 23–26). However, the long-term outcome was less favorable, with only six patients remaining completely off PPIs. Even so, there was still a relative improvement, as another five patients still experienced good symptom relief under PPI intake, whereas none was asymptomatic under PPI therapy at the time of the EG. In two patients with failed endoscopic gastroplication, subsequent antireflux surgery was performed uneventfully, as reported previously (27).

Although our study established a potential application of EG in patients with an incomplete response to medical therapy, additional studies will be required to determine its place in therapy. Being minimally invasive and reversible, the EG offers some interesting features compared to surgical fundoplication, and the procedure could be applied in selected patients who are less suitable for surgery. On the other hand, additional studies will be required to identify why some patients do not seem to respond to EG. Moreover, there seems to be a loss of efficacy between 3 and 12 months in our patient population, and clearly a longer follow-up of these patients will be required to establish whether any long-term efficacy is truly present.

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