

Modern GERD Treatment: Feasibility of Minimally Invasive Esophageal Sphincter Augmentation

KATRIN SCHWAMEIS^{1,3,4}, MICHAEL SCHWAMEIS², BARBARA ZÖRNER¹, JOHANNES LENGlinger¹, REZA ASARI^{1,3,4}, FRANZ MARTIN RIEGLER¹ and SEBASTIAN FRIEDRICH SCHOPPMANN^{1,3,4}

Departments of ¹Surgery and ²Clinical Pharmacology, ³Upper-GI Research Group, and ⁴Comprehensive Cancer Center Vienna (CCC-GET Unit), Medical University of Vienna, Vienna, Austria

Abstract. *Background:* Gastroesophageal reflux disease (GERD) is a common chronic disease requiring adequate treatment since it represents one major cause of development of Barrett's esophagus and eventually carcinoma. Novel laparoscopic magnetic sphincter augmentation for GERD was evaluated prospectively. *Patients and Methods:* A total of 23 patients with GERD underwent minimally invasive implantation of LINXTM Reflux Management System. Primary outcome measures were overall feasibility, short-term procedure safety and efficacy. Secondary GERD-related quality of life was assessed. *Results:* All implantations were performed without serious adverse events. A significant decrease in all major GERD complaints were found: heartburn: 96%-22% ($p<0.001$); bloating: 70%-30% ($p=0.006$); respiratory complaints: 57%-17% ($p=0.039$); sleep disturbance: 65%-4% ($p<0.001$). A four-week follow-up reduction of $\geq 50\%$ of proton pump inhibitor (PPI) dose was achieved in over 80% of patients. Self-limiting difficulty in swallowing was found in 70% within four weeks. One patient required for endoscopic dilation. GERD-related quality of life improved significantly. *Conclusion:* LINXTM implantation is a standardized, technically simple, safe and well-tolerated expeditious procedure.

Gastroesophageal reflux disease (GERD) represents an increasingly major health problem, affecting up to 20% of Western countries and even 44% of the US population intermittently (1, 2). Decreased quality of life and complications such as Barrett's esophagus and esophageal adenocarcinoma are associated with chronic GERD.

This article is freely accessible online.

Correspondence to: Professor Dr. Sebastian F. Schoppmann, Department of Surgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. Tel: +43 1404005621, Fax: +43 1404005641, e-mail: sebastian.schoppmann@meduniwien.ac.at

Key Words: LINXTM, GERD, reflux, esophageal sphincter, laparoscopy.

Adenocarcinoma of the esophagogastric junction (EGJ) is currently the most rapidly increasing solid malignancy, partially due to rising obesity rates, with a dramatic 650% increase in prevalence over the past decades (3). Therefore, sufficient therapy is urgently required.

The major pathological mechanism of GERD is a dysfunction of the lower esophageal sphincter (LES), which loses its competence to keep the gastric juice in the stomach, which consequently refluxes into the esophagus (4).

Early-stage GERD is symptomatically-treated with acid-suppressing proton pump inhibitors (PPIs), leading to sufficient long-term symptom relief in around 70% of patients (5). However, side-effects and the possible contribution of acid suppression promoting adenocarcinoma progression by engendering pro-inflammatory alkaline refluxate are ongoing matters of controversy (6-8).

Since its introduction in 1956, surgical fundoplication procedures have become the mainstays of therapy for patients suffering from advanced GERD refractory to medical treatment. Although currently gold standard when performed by experienced surgeons, the Nissen fundoplication and other surgical GERD therapies cause anatomical alterations, are non-reversible and have the potential for significant side-effects such as dysphagia, loss of belching and vomiting, increased flatulence and bloating (9, 5, 10).

Considering the deficiencies of current available therapies for symptomatic patients on PPIs and those who are between early-stage disease that is sufficiently treatable by conservative means and advanced reflux disorder with the need for Nissen fundoplication as the last resort, there is a great need for new therapeutic approaches and procedures (11).

Magnetic sphincter augmentation (MSA) intends to biomechanically-counteract the process of gastric distension with progressive dilation and acid-associated destruction of the distal esophagus by strengthening the barrier function of the LES, preventing its effacement with repetitive abnormal opening, subsequent reflux and progressive sphincter shortening (12, 11, 5, 13). A distensible metallic ring, consisting of a varying number of wire-connected titanium-cased beads, each

in turn enclosing a magnetic core, is placed around the EGJ to augment the barrier function of the LES (11, 14).

In the present report we share our perioperative short-term results on feasibility, safety and efficacy of implementing laparoscopic sphincter augmentation for GERD treatment at the Department of Surgery, Medical University of Vienna, Austria.

Patients and Methods

This prospective study aimed to assess the feasibility, safety and efficacy of laparoscopic sphincter augmentation with a new magnetic reflux device, the LINX™ Reflux Management System (Torax Medical Inc., Shoreview, Minnesota, USA), in the treatment of GERD.

The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, including the most recent revisions. The study protocol was approved by the local independent Ethical Committee of the Medical University of Vienna, Austria (ERC approval number 1434/2012).

Study population, eligibility criteria and therapeutic procedures. Patients, with GERD presenting at the specialized upper Gastrointestinal (GI) surgery outpatient clinic at the Department of Surgery, Medical University of Vienna, between January 2012 and May 2013, were screened according to the overall study protocol.

Study eligibility demanded verification of at least partial PPI-sensitive GERD, the continuity of reflux-related symptoms on PPI therapy, the absence of distinct esophageal motility disorders, of dysphagia, of diaphragmatic hernias of 3 cm or more, of esophagitis grade C or D in accordance to the Los Angeles classification, of Barrett's esophagus (15) and of allergies to the device's material. Furthermore, signed informed consent was requested from each patient.

Study appropriateness was assessed by a detailed registration of medical history and performance of endoscopy including biopsies (16). Furthermore, prior to surgery esophageal manometry and 24-h reflux monitoring was performed. For manometry, a 32-channel high-resolution impedance manometric system was used (InSight™; Sandhill Scientific, Highlands Ranch, CO, USA). Total and abdominal length of the pressure zone at the EGJ was measured. Expiratory resting pressure was recorded for over five respiratory cycles. Esophageal body motility was assessed with 10 liquid swallows of 5 ml at 30 second intervals.

Gastroesophageal reflux activity was monitored using a combined pH and impedance portable system (ZpHr™; Sandhill Scientific). Intraluminal pH was monitored at 5 cm proximal to the lower esophageal sphincter over 22 to 24 h. Procedures took place with patients pursuing their routine daily activities and dietary habits. PPI medication was discontinued 10 days prior to the tests.

GERD-related quality of life was measured at baseline and four weeks after sphincter augmentation using the Gastroesophageal Reflux Disease–Health-Related Quality of Life score (GERD-HRQL) comprising 10 distinct questions regarding GERD-related symptoms and their impact on life quality. Total scores range from 0 to 50, with lower scores indicating fewer symptoms (17).

Finally, between March 2012 and May 2013, 23 patients with chronic GERD were considered suitable and consecutively assigned to undergo laparoscopic LINX™ Reflux Management System implantation.

Surgical procedure and follow-up. Device implantation was performed laparoscopically using standard surgical techniques as described previously (12, 18). Briefly, after mobilization of the EGJ,

Table I. *Gastroesophageal reflux disease (GERD)-related complaints: Baseline vs. at four weeks postoperatively.*

Complaint	Baseline n (%)	4 Weeks n (%)	p-Value
Heartburn	22 (96)	5 (22)	<0.001*
Bloating	16 (70)	7 (30)	0.006*
Respiratory complaints	13 (57)	4 (17)	0.039*
Sleep disturbance	15 (65)	1 (4)	<0.001*
Changes in diet	17 (74)	2 (9)	<0.001*
Transient dysphagia	11 (48)	16 (70)	>0.1
Regurgitation	15 (65)	13 (57)	>0.1

*Statistically significant as outlined in the Patients and Methods section.

ring size was measured *via* a sizing tool and the appropriate magnetic ring was wrapped around the lower end of the esophageal sphincter.

All procedures were performed by the same surgeon and were standardized regarding surgeon's and patient's positions (anti-Trendelenburg), further trocar sites and used instruments.

Patients received a free diet postoperatively to avoid development of dysphagia due to scarred strictures. After at least one overnight stay, patients were discharged from Hospital once they were eating solid foods and showed a non-suspicious barium swallow.

Postoperative follow-up visits were performed routinely, including a detailed registration of symptoms and changes; furthermore the GERD-HRQL questionnaire was once more assessed after four postoperative weeks. Therefore, all given information on pre- and postoperative complaints represent symptoms subjectively perceived by patients.

Statistics. Statistical calculations were performed using IBM SPSS® Statistics for Windows, Version 20.0. IBM Corp, Armonk, NY, US. Continuous baseline values and demographic characteristics are expressed descriptively as means with standard deviations (SD), or medians with interquartile (IQ) ranges. For comparisons of pre- and postoperative data and quality of life scores, the paired Student's *t*-test and the Wilcoxon signed rank test were applied as appropriate, respectively. A two-sided *p*-value of 0.05 or less was considered to indicate statistical significance.

Results

Patients. Between March 2012 and May 2013, 23 patients underwent laparoscopic magnetic sphincter augmentation at the Department of Surgery, Medical University of Vienna. The study population comprised of 11 males and 12 females (median age=43 years; range=20 to 68 years) with an overall median body-mass index (BMI) of 26 (range=20-32). The median duration of reflux symptoms and of PPI intake at baseline were 4 years (range=1-20 years) and 1 year (range=<1-20 years), respectively. At baseline, two patients had already stopped their PPI intake due to severe side-effects, while another two patients were asymptomatic, but dissatisfied with the need for daily PPI medication.

Table II. Median gastroesophageal reflux disease (GERD) Health-Related quality of life (QoL) score: Baseline vs. four weeks postoperatively.

Questionnaire	Baseline	4 Weeks
How severe is your heartburn?	3.7	0.4
Do you have heartburn when lying down?	3.7	0.4
Do you have heartburn when standing up?	3.1	0.3
Do you have heartburn after meals?	3.7	0.3
Does heartburn change your diet?	3.1	0.7
Does heartburn wake you from sleep?	2.2	0.1
Do you have difficulty swallowing?	1.1	1.8
Do you have bloating and gassy feelings?	2	0.7
Do have pain on swallowing?	0.8	1.2
If you take medication, does this affect your daily life?	2.7	0.1
How satisfied are you with your present condition? (%)	0	83
Total median GERD score	29	4

Preoperative findings. Esophageal acid exposure was assessed by 24-h pH monitoring and the median total percentage of time with pH<4 was 4.4 h (range=0.9-17 h); mean±SD=5.8±4.5). For study inclusion, either an esophageal pathological acid exposure (34.8% of patients) or a positive symptom correlation was requested (65.2% of patients), as assessed by impedance.

No presence of relevant esophageal motility and LES disorders existed, as the mean percentage of effective swallows was 79.6% (range=0 to 100%) and the mean pressure in the distal esophagus was 95.7 mmHg (range=24 to 192 mmHg) in manometric findings.

Endoscopically, a mean hiatal hernia of 1.34 cm (range=0-2 cm) was measured. Five patients (21.7%) had signs of grade A esophagitis according to the Los Angeles classification. Most frequent GERD-related complaints were heartburn (95.7%) and abdominal fullness/bloating (69.6%). Furthermore, 48% of patients subjectively perceived difficulties in swallowing related to GERD at baseline (Table I). Due to the low GERD-related quality of life on PPIs, a 100% dissatisfaction rate regarding patients' medical condition was found and consequently the total GERD-HRQL score was high (median=29) (Table II).

Surgery. All 23 laparoscopic procedures were performed successfully within a median operative time (last port inserted to first port removed) of 23 min (range=9-42 min). Intraoperatively measured by sizing tool, the most frequently used ring size was 14 (range=12-16). In 10 out of 23 cases (43.5%), a harmonic scalpel was used. No intraoperative complications, such as bleeding or organ/tissue damage, occurred.

Postoperative findings. Nineteen patients (82.6%) were discharged within 48 h after implantation, while 12 of them (52%) left the hospital within 24 h. All patients completed the four-week follow-up. At this point, cessation of PPI use was

Table III. Postoperative adverse events.

Adverse event	Newly-occurring	Increased in severity	Total
Transient dysphagia	8	4	12
Odynophagia	5	3	8
Bloating	0	2	2
Heartburn	0	1	1
Sleep disturbance	0	1	1
Inability to belch or vomit	0	0	0

achieved in 71.4% (15/21), while two further participants (9.5%; 2/21) were able to halve their daily PPI dosage from day 1 postoperatively. Two patients were already off medication at baseline due to severe side-effects from PPIs. After four weeks, fewer than 20% of patients were still on PPIs. Significant reduction of primary GERD symptoms was shown for heartburn (96% to 22%; $p<0.001$), bloating/abdominal fullness (70% to 30%; $p=0.006$), respiratory complaints (57% to 17%; $p=0.039$) and sleep disturbance (65% to 4%; $p<0.001$) and regarding the necessity of staying on diet (74% to 9%; $p<0.001$) (Table I). The median GERD-HRQL score significantly improved from 29 to 4 ($p<0.001$) after sphincter augmentation and the percentage of patients who were satisfied with their health-related quality of life significantly increased from 0% to 74%; another 17.4% at least felt 'neutral', and 17% remained dissatisfied (Figure 1; Table II). Comparing patients with and those without pathological acid exposure at baseline, no relevant differences regarding quality of life improvements were found (Figure 2). About 74% ($n=17$) mentioned that they would highly recommend this procedure to family and friends and 13% ($n=3$) each felt neutral or would not chose this type of GERD surgery again due to lesser symptom relief than subjectively expected.

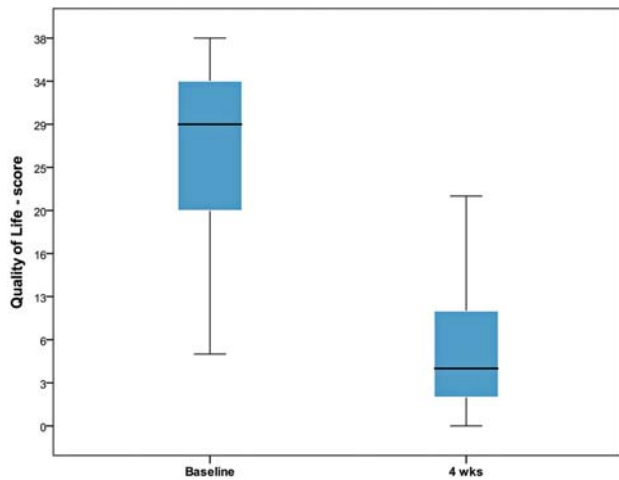


Figure 1. *Gastroesophageal reflux disease (GERD) Health-Related quality of life (QoL).*

Heartburn, as the most common preoperative complaint, completely resolved in 78.3% (18/23) (Figure 3, Table I). The other five participants (21.7%) remained symptomatic, although with lower severity (with a decrease in median severity score from 3 to 2), but an ongoing need for daily PPI intake in 60% of them. Neither belching nor vomit inableness was reported.

Seventy and fifty percent of patients reported as having had at least one mild period of difficulty in swallowing, painful swallowing or regurgitation, respectively, within the first four weeks after implantation. In all cases but one, which required endoscopic dilation, symptoms were self-limiting and resolved by follow-up at week four (Tables I and III, Figure 4). Any occurrence of new symptoms and any increase of severity of pre-existing symptoms within the four-week observation period were only temporary (Table III). No intra- or postoperative complications nor severe adverse effects occurred and no device removal or revision to Nissen fundoplication had to be performed.

Discussion

Although Nissen fundoplication remains the key surgical approach for patients with long-standing history of GERD, who only experience incomplete symptom resolution with chronic PPI use, its accomplishment is technically complex, with major alteration of normal anatomical structures. Debates on the potential long-term side-effects of PPIs, including vitamin malnutrition disorders, increased risk of bone fractures, *Clostridium difficile*-associated colitis (19) and pneumonia (20, 21), are ongoing, although particularly affecting susceptible vulnerable populations (22). However, considering the potential progression of GERD into

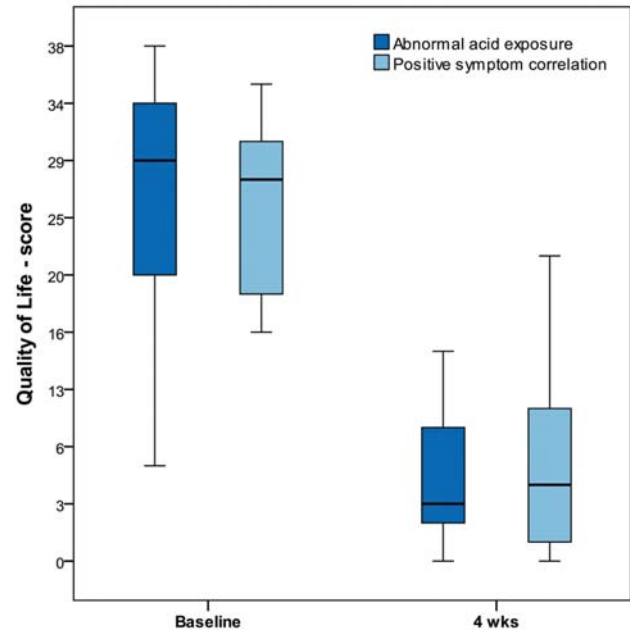


Figure 2. *Gastroesophageal reflux disease (GERD) Health-related quality of life (QoL) score in patients with and without pathological acid exposure at baseline and 4 week follow-up.*

adenocarcinoma, with LES incompetency to resist gastric distension and consequent progressive shortening as underlying key features, long-lasting use of PPIs as conservative GERD treatment appears inappropriate for disrupting this pathological vicious cycle. The clinical incapacity of acid-suppression therapy to completely resolve GERD-related complaints has led to the necessity of conceiving new therapeutic approaches.

The LINX™ reflux management system, as role model for MSA, was designed to provide a technically simpler, more reproducible and less operator-dependent therapeutic procedure for an out-patient setting to care for the needs of patients with GERD in whom the potential drawbacks of fundoplication may outweigh its benefits. Several recent studies provide long-term evidence for MSA being suitable for treating those patients. By mechanically strengthening the reflux barrier function of the LES, LINX™ appears to be appropriate for counteracting the pathogenic process underlying GERD by enhancing closure competence and reducing reflux.

Our short-term data largely match the results of previous trials demonstrating feasibility and longer-term safety of laparoscopic sphincter augmentation using standard laparoscopic techniques for appropriate indications. Firstly demonstrated in a live porcine model (14), good tolerability and safety of an MSA implant in men was shown in 2008 in a multi-center feasibility trial comprising a cohort of 38 patients

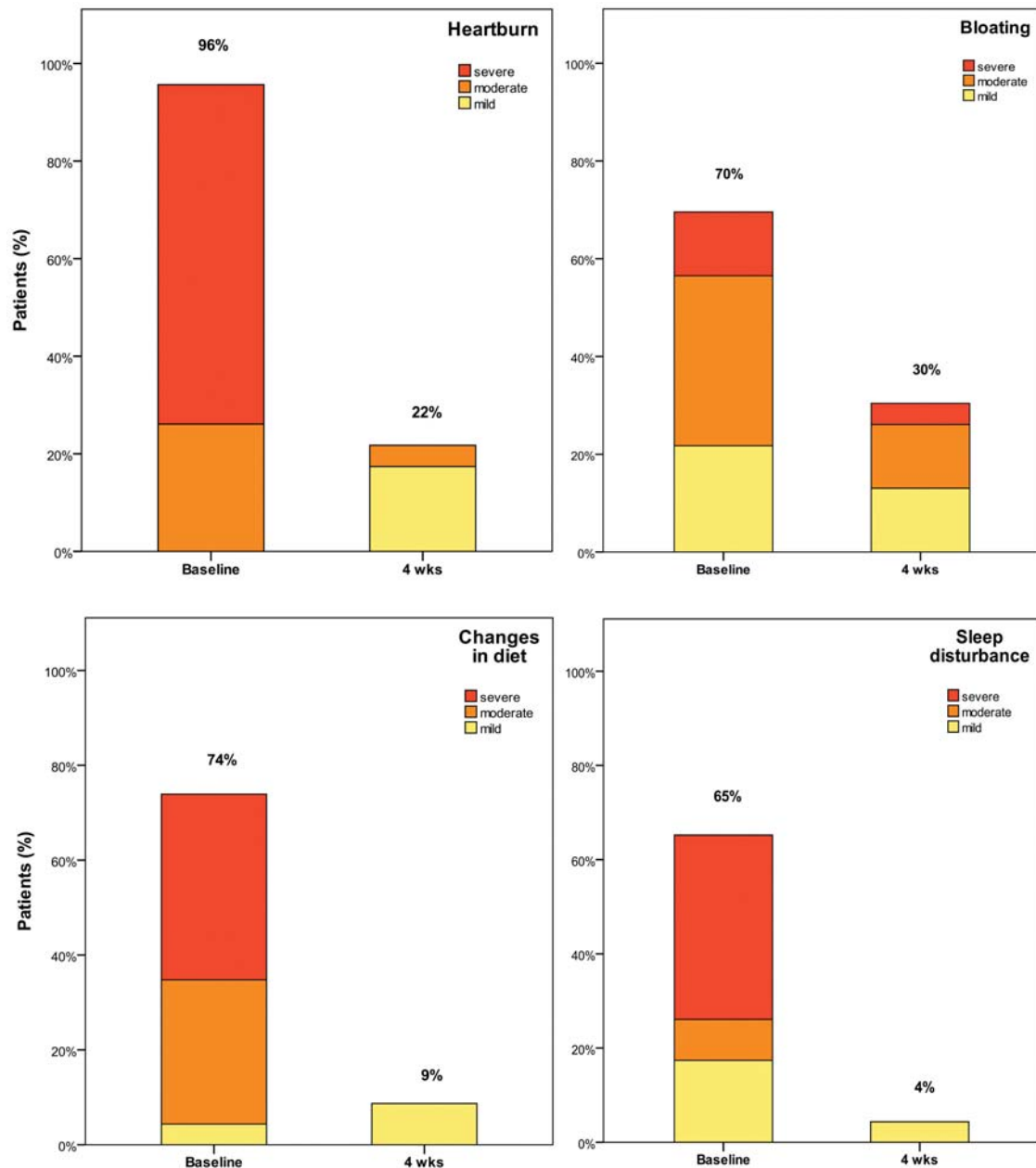


Figure 3. Complaints at baseline and four-week follow-up. Parameters were assessed as outlined in the Patients and Methods section.

with a one-year follow-up (11). Further trials succeeded and data on clinical experience with implanting the LINX™ system for GERD therapy are now available up to four years demonstrating sustained long-term clinical benefits without serious safety issues (18). Confirming these findings, very recently, Ganz *et al.* published their three-year outcome results of a prospective, multi-center, single-group trial on 100 patients, also addressing safety and effectiveness of MSA, showing an achievement of acid exposure normalization in

64% of patients, with a reduction of 50% or more in the use of PPIs in 93%, and a 92% improvement of 50% or more in quality-of-life scores, with serious adverse events in 6%, need for device removal in six patients and dysphagia as the most frequent side-effect (4% at three years) (5).

Accordingly, the short-term-outcome of this series shows significant improvements in GERD-related quality of life (median score=29 to 4; $p<0.000$) due to significant reduction of all major GERD-related symptoms, resulting in a 74%

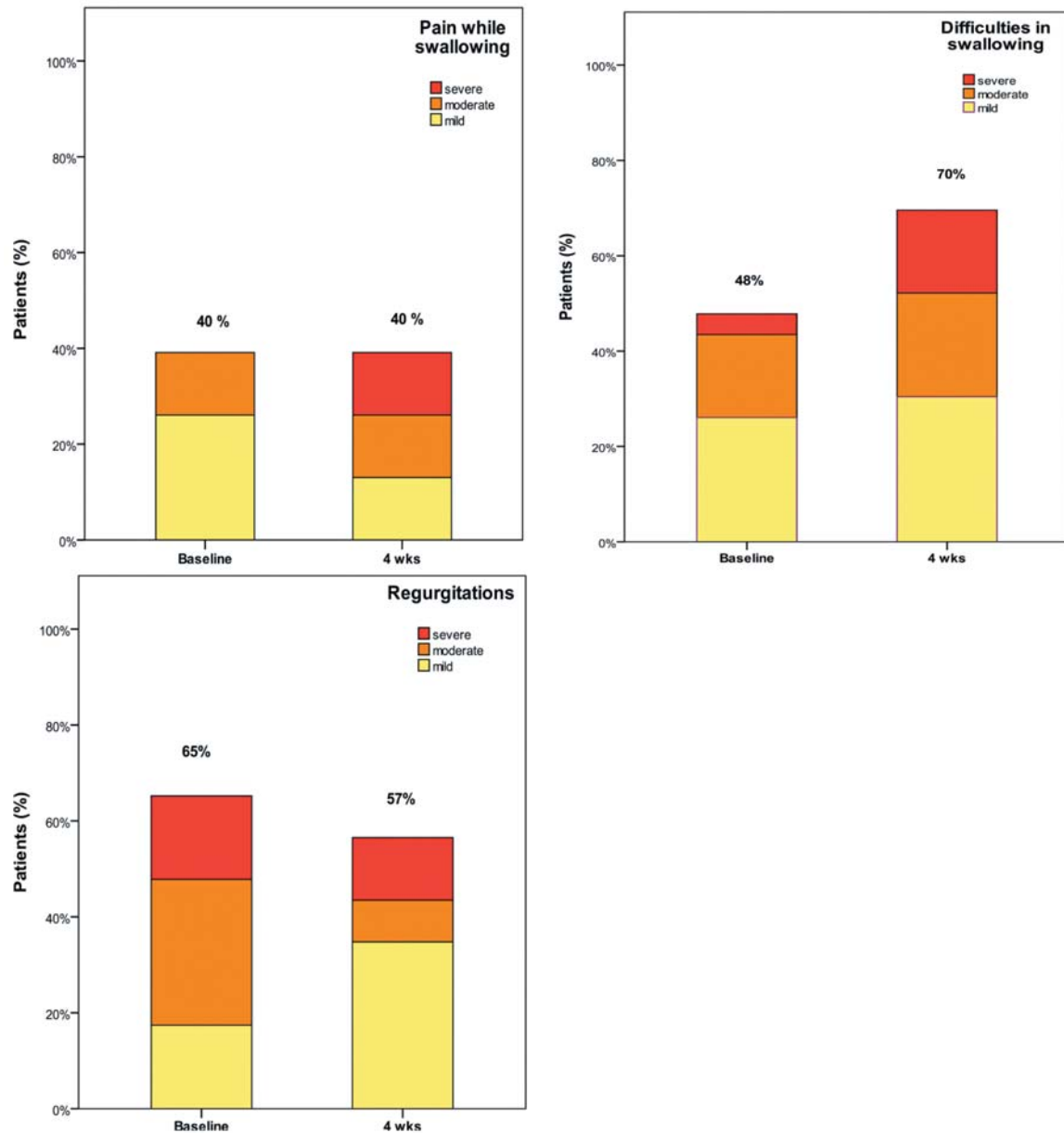


Figure 4. Dysphagia, odynophagia and regurgitation as the most common side effects following laparoscopic sphincter augmentation.

increased satisfaction rate regarding medical condition, accompanied by an equally high retrospective recommendation rate for this procedure. Not only patients with objective abnormal acid exposure, but also those who experienced a distinct positive symptom correlation, showed a similar significant improvement in life quality when analyzed separately (Figure 4).

A cessation (71.4%) or a dose reduction of 50% or more (9.5%) in PPI use was registered in over 80% of patients, indicating adequate symptom relief, or at least significant

symptom reduction, as a result of sphincter augmentation.

No relevant intra- or perioperative complications or severe postoperative side-effects were found in the present study. We strictly asked patients about any subjectively perceived occurrence of difficulty swallowing within the first four weeks after implantation and up to 70% stated as having had at least one mild period. These self-limiting difficulties in swallowing represent the most common adverse events in this trial, but were offset by the significant overall increase in life quality. As can also occur after fundoplication, early postoperative

dysphagia after sphincter augmentation has been multiply reported as being mostly self-limiting and spontaneously resolving without need for intervention (12). Only one patient in our series finally had to undergo dilatation endoscopically due to prolonged dysphagia, while the rest were only temporary and resolved without therapy. A settling-in period after LINX™ ring placement therefore seems fairly warranted, unless intractable disabling difficulties in swallowing occur.

Overall, the frequency of regurgitation decreased: while 65% of patients suffered from this at baseline, it occurred in only 57% within the first four weeks postoperative and cases of new onset were self-limiting (4/23; 17.4%). At the week 4 follow-up, nine patients (39.1%) still intermittently experienced regurgitation.

All subjective symptoms newly-occurring or increasing in severity normalized within the observation period of four weeks.

Advantageously, according to the device's dynamic function, vomiting and belching are not inhibited as they are after fundoplication. Thus, postoperative flatulence and bloating are not to be expected after MSA. We recorded a significant decrease in the frequency of bloating after ring implantation by 40% at four weeks.

Corresponding to the learning curve, we experienced a significant shortening of the operative time after familiarization with the device fastening. At this point, MSA is much faster (mean operative time=23 min) than a standard fundoplication.

Although hospital discharge was performed very carefully and late in this implementation phase (hospital stay >24 hours in 48% of patients), this study suggests no need for a hospitalization longer than 24 h after MSA.

Even though not directly comparable with results after fundoplication, due to a different patient population, there are no obvious indices for disadvantages after MSA.

Key to successful MSA is correct preoperative patient selection and this will lead to satisfaction in patients with earlier GERD stages, who are still symptomatic despite PPI intake and show no presence of larger hiatal hernias or severe mucosal and LES damage, since this represents advanced-stage disease. Due to less anatomical alteration caused by MSA, explantation and revision into fundoplication remains feasible at any point, while primary fundoplication inhibits a procedure switch to ring implantation.

Future trials need to relax current exclusion criteria such as hiatal hernia size <3 cm in order to precisely investigate and characterize all those patients who could benefit from sphincter augmentation, so as to expand its currently limited applicability.

Conclusion

Laparoscopic sphincter augmentation is a novel minimally invasive approach for the surgical treatment of patients with GERD with only partial symptom relief on PPI medication. Our study provides reinforced evidence for its feasibility and safety within the perioperative phase of four weeks,

considering the LINX™ device appropriate for use in an outpatient procedure.

Short-term outcomes of this trial suggest that MSA leads to efficient GERD symptom relief, and adequate reduction of PPI need, while procedure-related side-effects are self-limiting in the majority of patients. Thus, GERD-related quality of life increased significantly, as did patients' satisfaction with their health status.

Minimal invasiveness, reversibility, outpatient applicability and preservation of normal anatomical structures, accomplished with retained ability to belch and vomit, thereby lacking flatulence and bloating as typical side-effects of fundoplication, make laparoscopic sphincter augmentation an encouraging therapeutic option for accurately evaluated patients. The metallic ring's potential incompatibility with magnetic resonance imaging is certainly a considerable issue which remains to be addressed. Extension of application to patients with hiatal hernia larger than 3 cm, combined with hernial repair seems a future possibility.

Since our short-term results are promising, data on long-term outcome after endoscopic sphincter augmentation are eagerly awaited.

Sources of Support and Disclosure of Funding

Dr. Sebastian Friedrich Schoppmann received an unrestricted research grant from TORAX® Medical Inc.

References

- 1 McCann S, Grant AM, Krukowski ZH and Bruce J: Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane database of systematic reviews: CD003243, 2010.
- 2 Wu P, Zhao XH, Ai ZS, Sun HH, Chen Y, Jiang YX, Tong YL and Xu SC: Dietary intake and risk for reflux esophagitis: a case-control study. *Gastroenterol Res Pract*: 691026, p9, 2013.
- 3 Cook MB, Shaheen NJ, Anderson LA, Giffen C, Chow WH, Vaughan TL, Whiteman DC and Corley DA: Cigarette smoking increases risk of Barrett's esophagus: an analysis of the Barrett's and Esophageal Adenocarcinoma Consortium. *Gastroenterology* 142: 744-753, 2012.
- 4 Chandrasoma P, Wijetunge S, Ma Y, Demeester S, Hagen J and Demeester T: The dilated distal esophagus: A new entity that is the pathologic basis of early gastroesophageal reflux disease. *Am J Surg Pathol* 35: 1873-1881, 2011.
- 5 Ganz RA, Peters JH, Horgan S, Bemelman WA, Dunst CM, Edmundowicz SA, Lipham JC, Luketich JD, Melvin WS, Oelschlager BK, Schlack-Haerer SC, Smith CD, Smith CC, Dunn D and Taiganides PA: Esophageal sphincter device for gastroesophageal reflux disease. *N Engl J Med* 368: 719-27, 2013.
- 6 Kastelein F, Spaander MC, Steyerberg EW, Biermann K, Valkhoff VE, Kuipers EJ, Bruno MJ; ProBar Study Group. Proton pump inhibitors reduce the risk of neoplastic progression in patients with Barrett's esophagus. *Clin Gastroenterol Hepatol* 11: 382-388, 2013.

- 7 Miyashita T, Shah FA, Harmon JW, Marti GP, Matsui D, Okamoto K, Makino I, Hayashi H, Oyama K, Nakagawara H, Tajima H, Fujita H, Takamura H, Murakami M, Ninomiya I, Kitagawa H, Fushida S, Fujimura T and Ohta T: Do proton pump inhibitors protect against cancer progression in GERD? *Surg Today* 43: 831-837, 2012.
- 8 Nasr AO, Dillon MF, Conlon S, Downey P, Chen G, Ireland A, Leen E, Bouchier-Hayes D and Walsh TN: Acid suppression increases rates of Barrett's esophagus and esophageal injury in the presence of duodenal reflux. *Surgery* 151: 382-390, 2012.
- 9 Finks JF, Wei Y and Birkmeyer JD: The rise and fall of antireflux surgery in the United States. *Surgical endoscopy* 20: 1698-1701, 2006.
- 10 Wang YR, Dempsey DT and Richter JE: Trends and perioperative outcomes of inpatient antireflux surgery in the United States, 1993-2006. *Diseases of the esophagus: official journal of the International Society for Diseases of the Esophagus/ISDE* 24: 215-223, 2011.
- 11 Bonavina L, Saino GI, Bona D, Lipham J, Ganz RA, Dunn D and DeMeester T: Magnetic augmentation of the lower esophageal sphincter: Results of a feasibility clinical trial. *J Gastroint Surg* 12: 2133-2140, 2008.
- 12 Bonavina L, DeMeester T, Fockens P, Dunn D, Saino G, Bona D, Lipham J, Bemelman W and Ganz RA: Laparoscopic sphincter augmentation device eliminates reflux symptoms and normalizes esophageal acid exposure: one- and 2-year results of a feasibility trial. *Ann Surg* 252: 857-862, 2010.
- 13 Smith K: GERD. Feeling the pull: a new device for sphincter augmentation. *Nat Rev Gastroenterol Hepatol* 10: 198, 2013.
- 14 Ganz RA, Gostout CJ, Grudem J, Swanson W, Berg T and DeMeester TR: Use of a magnetic sphincter for the treatment of GERD: a feasibility study. *Gastrointest Endosc* 67: 287-294, 2008.
- 15 Mesteri I, Beller L, Fischer-See S, Schoppmann S, Lenglinger J, Wrba F, Riegler M and Zacherl J: Radiofrequency ablation of Barrett's esophagus and early cancer within the background of the pathophysiology of the disease. *Eur Surg* 44: 366-382, 2012.
- 16 Mesteri I, Lenglinger J, Beller L, Fischer-See S, Schoppmann SF, Wrba F, Riegler FM and Zacherl J: Assessment of columnar-lined esophagus in controls and patients with gastroesophageal reflux disease with and without proton-pump inhibitor therapy. *Eur Surg* 44: 304-313, 2012.
- 17 Velanovich V: Comparison of generic (SF-36) vs. disease-specific (GERD-HRQL) quality-of-life scales for gastroesophageal reflux disease. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract* 2: 141-145, 1998.
- 18 Lipham JC, DeMeester TR, Ganz RA, Bonavina L, Saino G, Dunn DH, Fockens P and Bemelman W: The LINXTM reflux management system: confirmed safety and efficacy now at 4 years. *Surg Endosc* 26: 2944-2949, 2012.
- 19 Scheurlen M: Long-term use of proton pump inhibitors: who needs prophylaxis?. *Internist* 54: 366-372, 2013 (in German).
- 20 de Jager CP, Wever PC, Gemen EF, van Oijen MG, van Gageldonk-Lafeber AB, Siersema PD, Kusters GC and Laheij RJ: Proton pump inhibitor therapy predisposes to community-acquired *Streptococcus pneumoniae* pneumonia. *Aliment Pharmacol Ther* 36: 941-949, 2012.
- 21 Jena AB, Sun E and Goldman DP: Confounding in the association of proton pump inhibitor use with risk of community-acquired pneumonia. *J Gen Intern Med* 28: 223-230, 2013.
- 22 Triadafilopoulos G, Roorda A and Akiyama J: Indications and safety of proton pump inhibitor drug use in patients with cancer. *Expert Opin Drug Saf* 5: 659-672, 2013.

Received November 25, 2013

Revised February 4, 2014

Accepted February 6, 2014