Objective Evidence of Reflux Control After Magnetic Sphincter Augmentation

One Year Results From a Post Approval Study

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Objective: To report 1-year results from a 5-year mandated study.

Summary Background Data: In 2012, the United States Food and Drug Administration approved magnetic sphincter augmentation (MSA) with the LINX Reflux Management System (Torax Medical, Shoreview, MN), a novel device for the surgical treatment of gastroesophageal reflux disease (GERD). Continued assessment of safety and effectiveness has been monitored in a Post Approval Study.

Methods: Multicenter, prospective study of patients with pathologic acid reflux confirmed by esophageal pH testing undergoing MSA. Predefined clinical outcomes were assessed at the annual visit including a validated, disease-specific questionnaire, esophagogastricduodenoscopy and esophageal pH monitoring, and use of proton pump inhibitors.

Results: A total of 200 patients (102 males, 98 females) with a mean age of 48.5 years (range 19.7–71.6) were treated with MSA between March 2013 and August 2015. At 1 year, the mean total acid exposure time decreased from 10.0% at baseline to 3.6%, and 74.4% of patients had normal esophageal acid exposure time (% time pH<4 ≤5.3%). GERD Health-Related Quality of Life scores improved from a median score of 26.0 at baseline to 4.0 at 1 year, with 84% of patients meeting the predefined success criteria of at least a 50% reduction in total GERD Health-Related Quality of Life score compared with baseline. The device removal rate at 1 year was 2.5%. One erosion and no serious adverse events were reported.

Conclusions: Safety and effectiveness of magnetic sphincter augmentation has been demonstrated outside of an investigational setting to further confirm MSA as treatment for GERD.

Keywords: gastroesophageal reflux disease, LINX, magnetic sphincter augmentation, proton pump inhibitors, quality of life

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For over half a century, the treatment options for patients with chronic gastroesophageal reflux disease have been dominated by 2 primary options: Nissen fundoplication and antisecretory medications—first with histamine receptor antagonists and later with proton pump inhibitors.[1] The overwhelming majority of patients receive medical therapy, but uncertainties persist about the long-term risks of proton-pump inhibitors (PPIs) and substantial portions of patients have inadequate symptom control despite PPIs.[2–4] Nissen fundoplication provides an effective antireflux barrier but concerns persist about its long-term efficacy and the potential side effects that are created. There remains a need for an effective therapy that

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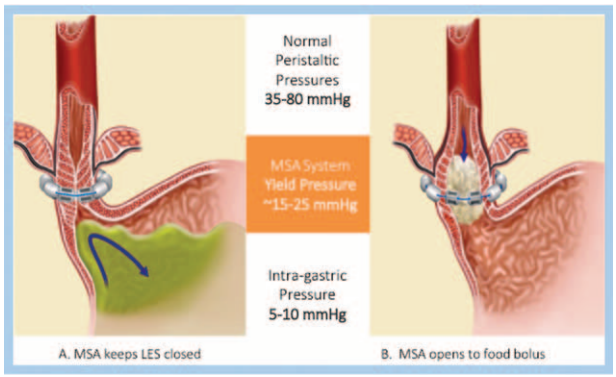

FIGURE 1. Magnetic Sphincter Augmentation with the LINX Reflux Management System. A, MSA at rest in the closed position. It is noncompressive and controls reflux by resisting sphincter opening due to gastric challenges (ie, magnetic force>gastric pressure). B, MSA in the open position. The bead's magnetic attraction is overcome by bolus pressures, which allows the device to open (ie, the bolus pressure >magnetic attraction). This is transient though, as the swallow pressure drops, the device will be drawn closed by the magnetic attraction. MSA indicates magnetic sphincter augmentation.

addresses the underlying problem, a defective lower esophageal sphincter, to control refluxed gastric contents that is more acceptable to patients and their referring physicians.

In 2012, the United States Food and Drug Administration (FDA) approved magnetic sphincter augmentation (MSA) with the LINX Reflux Management System (Torax Medical, Shoreview, MN), a novel minimally invasive device for the surgical treatment of gastroesophageal reflux disease (GERD) (Fig. 1A, B). A series of studies were conducted in support of regulatory approval of LINX which provided valid scientific evidence of safety and effectiveness for magnetic sphincter augmentation for the treatment of GERD.[5–8] These studies demonstrated that a short laparoscopic procedure to implant the device around the gastroesophageal junction while leaving the gastric fundus intact provides effective control of reflux symptoms and maintains normal physiologic functions, such as food bolus transit, belching, and vomiting. As part of an ongoing assessment of magnetic sphincter augmentation in clinical practice, LINX has been monitored as part of the FDA approval process in a mandated Post Approval Study to confirm clinical outcomes achieved in the setting of a controlled, investigational study can also be achieved in broader clinical practice (NCT01940185). Here we report the clinical results at 1 year.

METHODS

Study Population

Patient selection was similar to the FDA investigational studies (NCT 01058070; NCT 00776997) and included pathological GERD as confirmed by ambulatory esophageal pH testing and persistent GERD symptoms, which were not controlled or only partially controlled by acid suppression therapy. Patients were generally not considered for MSA if presurgical screening indicated: effective swallows were <70% and distal amplitude <35 mm Hg; presence of major motility disorders; gross esophageal anatomic abnormalities; hiatal hernia ≥3 cm, erosive esophagitis grade C or D (Los Angeles Classification); body mass index >35; Barrett esophagus; or allergy to titanium, stainless steel, nickel, or ferrous materials. However, only the allergies are actual contraindications to enrollment and implantation of the device. A patient with GERD with one of the above precautions could be deemed to be a candidate for MSA at the discretion of the enrolling surgeon.

Study Design

This multicenter, prospective, study was designed with input from the FDA and evaluated patients with GERD before and after MSA with predefined clinical measures. Participating sites were selected based on their dedicated interest in the surgical treatment for GERD as well as an adequate patient volume to support enrollment of patients into the study. Participating physicians were qualified by education, training, and surgical experience. All participating study centers were required to have undergone training to implant the device and completed a minimum of 5 LINX implants. The majority of surgeons/centers (11/17) selected had not participated in the prior MSA regulatory trials. The enrollment by site is listed in Table 1.

Patients were recommended to have the following assessments prior to surgery: (1) recent esophageal pH monitoring performed off acid-suppression therapy to confirm the diagnosis of GERD; (2) high-resolution manometry to assess motility; and (3) an upper gastrointestinal endoscopy to assess the presence of esophagitis, Barrett esophagus, and hiatal hernia.

During the initial screening phase, patients were evaluated for their GERD medication usage and completed the Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) questionnaire[9] and the Foregut Symptom Questionnaire (FSQ)[10] after discontinuation of PPIs and histamine-2 receptor antagonists for at least 7 days and antacids up till the morning of the assessment. Quality of life questionnaires, along with review of PPI use and esophageal pH testing, were evaluated at 1 year, with additional annual follow-up planned through 5 years after implant. Each site is monitored and visited by the study coordinators on a regular schedule each year with all study patients enrolled in the study having their data verified against source documentation. The questionnaires, upper endoscopy and esophageal pH monitoring are assessed off medication at the annual visits. The institutional review board of each participating institution approved the study protocol, and all patients signed an informed consent document.

TABLE 1. Enrollment by Center

Site	Number of Subjects
Swedish Medical Center—Seattle	31
Esophageal Institute of Atlanta	26
Albany Surgical	20
SurgOne Foregut Institute	19
Virginia Heartburn and Hernia Institute	18
South Coast Health	19
Ohio State University	13
Bingham Memorial Hospital	11
Knox Regional Heartburn Treatment Center	11
Oregon Clinic	8
Cuyuna Regional Medical Center	5
University of Southern California	4
University Hospitals Case Medical Center	4
University of Nevada	3
Allegheny Health Network	3
Gundersen Health System	3
Medical College of Wisconsin	2
Total	200

Effectiveness and Safety Assessments

The effectiveness of the device was assessed using both subjective and objective measurements to evaluate the response of surgery compared with baseline.

For the FDA continuing review of MSA, the primary effectiveness outcome was patient quality of life as measured by the GERD-HRQL questionnaire.[9] The validated GERD-HRQL assesses GERD symptoms and patient satisfaction using a 0 to 5 rating scale. It is composed of 10 questions relating to severity of heartburn symptoms while lying down, standing up, after meals, after a change in diet, while sleeping and severity of symptoms related to GERD including dysphagia, odynophagia, bloating, and effect of medications. The total GERD-HRQL score is calculated by summing the responses to 10 questions; possible scores range from 0 (ie, asymptomatic in each item) to 50 (incapacitated in each item). A $\geq 50\%$ improvement in the total GERD-HRQL score compared with the baseline off PPIs was considered clinically significant.

The FSQ queried patients about ability to belch and vomit as well as extra-esophageal symptoms. Additionally, questions from the GERD-HRQL for gassy/bloating feeling, difficulty swallowing, and painful swallowing were evaluated at baseline and at 1 year to determine the percentage of patients who reported bothersome symptoms occurring at least daily (score ≥ 3).

Additional effectiveness outcomes included esophageal acid exposure, PPI usage, regurgitation, and extraesophageal symptoms. Successful reduction in esophageal acid exposure at 1 year was met if the total % time was normal (pH<4 for $\leq 5.3\%$), or if a patient had at least a 50% reduction in total % time at 1 year compared with baseline. Normal esophageal acid exposure was defined as the total % time pH < 4 was $\leq 5.3\%$. Use of PPIs during the last 30 days was recorded at each visit.

Serious adverse events and device removals related to MSA were carefully monitored throughout the study starting at the time of device implant and proceeding throughout the duration of the follow-up period. Serious adverse events were defined as complications that were life threatening, necessitating in-patient or prolongation of hospitalization, or resulted in death or permanent disability.

Statistical Analysis

Outcome data were analyzed by an independent biostatistician using SAS software (SAS Institute, Cary, NC). Sample size of the study was determined by considering probability of detecting rare events, with a rare event defined as one with an underlying incidence of 2% or less. The probability of detecting 1 or more rare events with 200 implanted study patients is $> 98\%$. A potential lost to follow-up rate of 25% prior to 5 years follow-up was assumed, leaving the probability of detecting 1 or more rare events among those with complete follow-up at $> 95\%$. Therefore, a minimum study size of 200 study patients was selected. Continuous outcomes such as esophageal acid exposure were evaluated by computing the difference between baseline and 1 year values and applying the Wilcoxon signed rank test. Mean and standard deviation (SD) were used to describe continuous outcomes as well as changes from baseline measurements. Median with interquartile ranges was used when a non-normal distribution was encountered. Categorical outcomes were summarized via frequency distributions. For all outcome data, differences were considered significant at the 0.05 level.

RESULTS

Patient Characteristics

A total of 200 patients (102 males, 98 females) were treated with MSA between March 2013 and August 2015 at 17 clinical centers in the United States. Average enrollment per center was 12 patients. The enrolled patients had a mean age of 48.5 years old (range 19.7–71.6) with a mean body mass index of 27.4 (range 18.0–39.0). Overall, the patients had a history of GERD for a mean duration of 11.9 years (range 0.5–50.0) and were utilizing PPI therapy for a mean duration of 8.5 years (range 0.5–30.0).

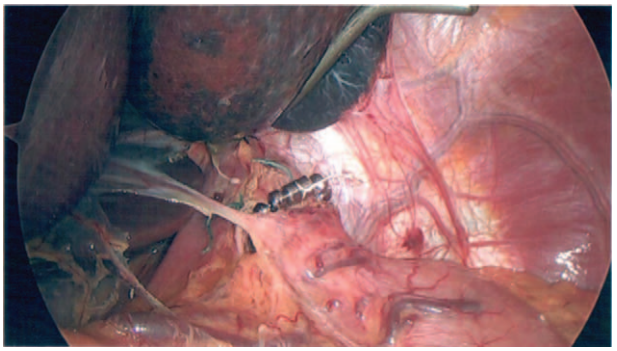

FIGURE 2. Intraoperative view of MSA after laparoscopic implantation. MSA indicates magnetic sphincter augmentation.

The median baseline GERD-HRQL total score was 26.0 and 95% of patients reported being dissatisfied with their present condition. Baseline endoscopic assessment showed no esophagitis in 74.7% of patients, LA Classification Grade A in 18.2%, Grade B in 5.6%, Grade C in 1.0% and Grade D in 0.5%. No patients had a hiatal hernia > 3 cm by endoscopic evaluation. The patients with body mass index >35 ($n = 6$) and esophagitis Grade C and D ($n = 3$) were included in the data analysis.

Procedure and Discharge

All patients were successfully implanted using a standard laparoscopic approach to place the device at the gastroesophageal junction (Fig. 2). There were no intraoperative complications. Concomitant hiatal hernia or crural repair was performed in 33.5% of patients. Ninety-one percent of patients were discharged within 24 hours of the procedure on a normal diet.

Follow-up 1 Year After MSA

Follow-up data (GERD-HRQL score, esophageal pH monitoring, medication use, and/or safety assessment) were available for 91% of patients (182/200) at 1 year including 1 patient who underwent removal of the device just after completing the 1-year follow-up. For the patients without a 1-year follow-up: 4 patients underwent removal of the device prior to 1 year of follow-up and exited from the study; 13 patients missed the follow-up visit and remain enrolled; and 1 patient was lost to follow-up.

Effectiveness

The predefined study success criteria of achieving a 50% or greater reduction in total GERD-HRQL score was achieved by 84.3% of patients at 1 year (95% exact binomial confidence interval 78.0, 89.4). Median GERD-HRQL scores improved from 26.0 ($SD \pm 6.5$) before MSA to 4.0 ($SD \pm 9.7$) at 1 year. When asked about satisfaction with present condition, 80% replied satisfied, 15% replied neutral, and 5% replied dissatisfied. In the 5% of dissatisfied patients ($n = 10$), the median total % time pH<4 was 5.1 (IQR = 3.7–5.6) while the median GERD-HRQL was 18 (IQR = 16–24).

Of the 164 patients agreeing to complete esophageal pH monitoring, 76.8% (95% confidence interval 70.4, 83.3) achieved successful reduction in esophageal acid, 74.4% (95% confidence interval 67.7, 81.1) had normal esophageal acid exposure, and 72.4%

TABLE 2. Esophageal pH Measurements and DeMeester Score

pH Result Mean (Range)	Baseline n = 197	One Year n = 164	*P* Value*
Total % time pH<4	10.0 [2.0, 32.9]	3.6 [0.0, 19.0]	<0.0001
Upright % time pH<4	12.1 [0.8, 33.5]	4.7 [0.0, 26.1]	<0.0001
Supine % time pH<4	6.0 [0.0, 39.4]	1.9 [0.0, 17.8]	<0.0001
Total number of reflux episodes	72.2 [9.6, 243.2]	22.6 [0.0, 111.4]	<0.0001
Number of reflux episodes >5 min	6.1 [0.0, 37.1]	2.2 [0.0, 14.6]	<0.0001
Longest reflux episode	30.6 [2.0, 134.0]	14.3 [0.0, 83.0]	<0.0001
DeMeester score	33.4 [8.7, 113.0]	12.0 [0.2, 59.7]	<0.0001

All parameters show statistically significant reduction from baseline with $P < 0.0001$. Some parameters show non-normality but P values are still < 0.0001 if a nonparametric Wilcoxon test is additionally applied.

(95% confidence interval 65.5, 79.3) had a normal DeMeester Score. Mean % time pH < 4 decreased from 10.0% at baseline to 3.6% at 1 year ($P = <0.001$). All components of esophageal monitoring and the DeMeester Score showed statistically significant reduction from baseline compared with 1 year (Table 2).

Overall, 87.4% of patients have completely discontinued PPIs, and 91.4% of patients are free from daily PPI use. A total of 22 patients reported using PPIs as needed (7), daily (10), and twice daily (5). The median GERD-HRQL was 7 (IQR = 1–17). Of the 22 patients on PPIs, 17 underwent pH testing at 12-month follow-up with a median % time pH < 4 = 2.1 (IQR = 0.6–7.3) and 12 patients having normal %time pH < 4 (normal < 5.3%). Eighty percent of patients taking PPIs as needed had a normal % time pH < 4, those taking daily PPIs 56% and those taking twice daily PPIs 100%.

Regurgitation and extra-esophageal symptoms assessed by the FSQ showed improvement after MSA, with the majority of patients (61.5%) at baseline reporting moderate/severe regurgitation compared with 5.4% at 1 year, and with extra-esophageal symptoms improving for recurrent cough, nocturnal cough and change of voice (Figs. 3, 4).

Side Effects and Safety

The ability to belch and vomit (when needed) was maintained by 99% and 93% of patients, respectively. Of patients self-reporting by the validated GERD-HRQL, symptoms of gas/bloat, difficulty swallowing, and painful swallowing, showed improvement of these symptoms at 1 year when compared with baseline (Fig. 5). A total of 82 patients reported no swallowing difficulties at baseline. Post MSA, 30 (36.6%) patients reported symptoms of dysphagia at the 12-month follow-up. Of those, 14 of 30 reported noticeable but not bothersome symptoms; 12 of 30 reported noticeable and bothersome symptoms but not everyday; 3 of 30 reported bothersome symptoms everyday; and 1 patient had daily symptoms affecting daily activities. Post MSA dilation was required in 13 of these patients with symptomatic resolution in 76.9% (10/13). One subject (7.7%, 1/13) exited the study prior to providing an update to their dysphagia event. Two (15.4%, 2/13) of these dysphagia events remain ongoing.

No life-threatening events, deaths, or permanent disability occurred during the 1-year safety assessment. Additionally, no new risks or unanticipated adverse device effects were reported. Four patients (2%) were readmitted within 30 days of the implant procedure for either dysphagia, nausea, or vomiting. Five patients (2.5%) had the device removed. Removal was performed for vomiting (11 days post implant), dysphagia (243 and 323 days post implant), device erosion (362 days post implant), or pseudo achalasia (343 days post implant). Device removals were safely performed in all cases by a laparoscopic or endoscopic approach with no sequelae. The only patient with device erosion presented with new onset dysphagia and odynophagia but with no GERD symptoms about

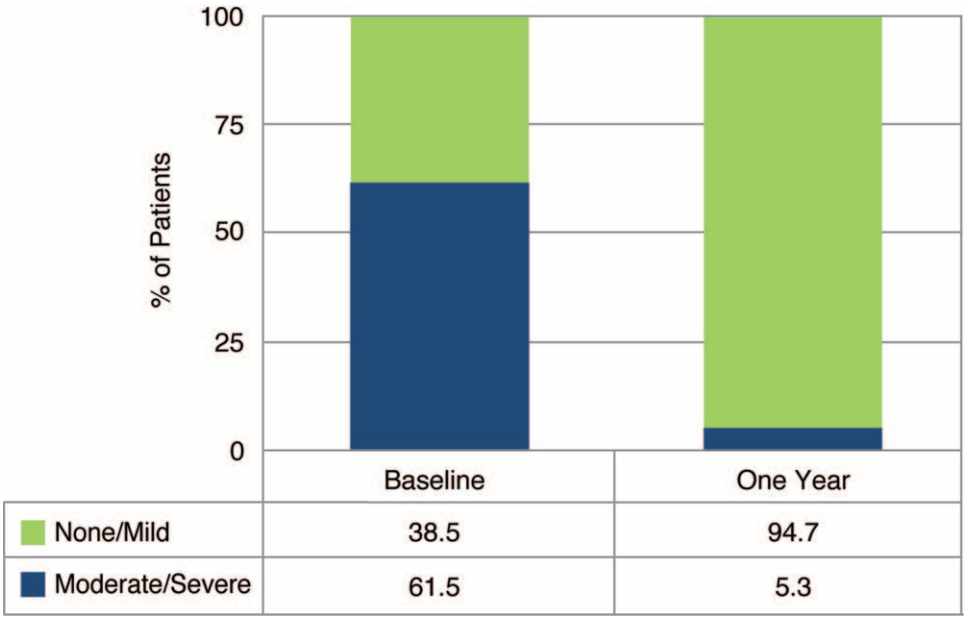

FIGURE 3. Percent of patients presenting with none/mild or moderate/severe regurgitation at baseline compared with 1-year postimplant.

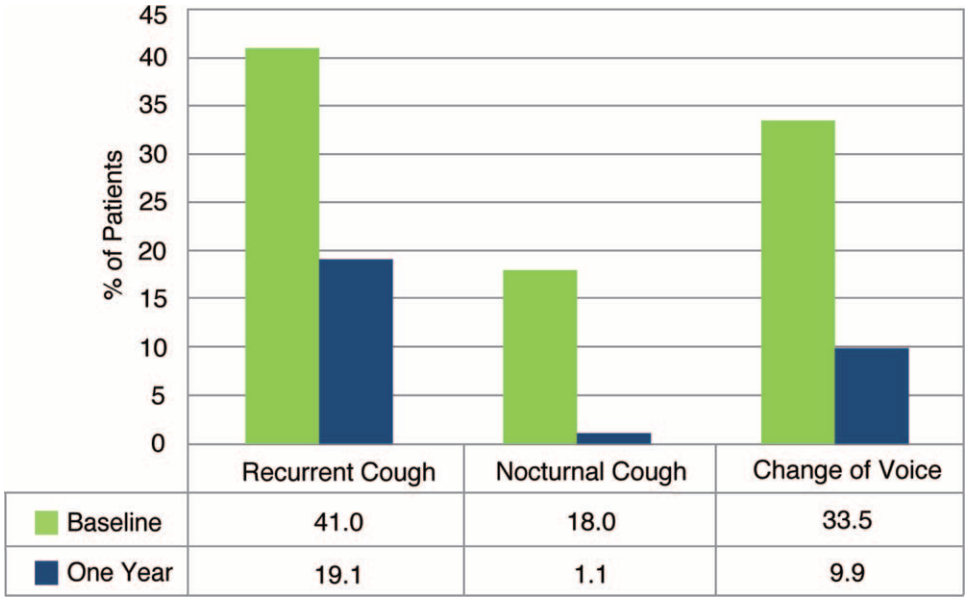

FIGURE 4. Patient reporting of extra-esophageal symptoms at baseline and at 1-year postimplant.

1 year after implant. A barium esophagram and upper endoscopy revealed partial erosion of beads into the esophageal lumen. The device was removed in its entirety by an endoscopic approach, without complication or in-patient hospitalization. At 30 days post explant, the patient's dysphagia and odynophagia had completely resolved and had not developed symptoms of GERD. Two patients with device removal elected to have another antireflux procedure. One had a Nissen fundoplication after device removal for dysphagia, and the other had a Toupet fundoplication after device removal for pseudo achalasia. The remaining 2 patients elected to resume PPIs.

DISCUSSION

The primary finding in this FDA mandated postapproval study is that magnetic sphincter augmentation 1 year after implantation significantly improved the patients' GERD quality of life, normalized the esophageal acid exposure and achieved freedom from PPIs. These results add to the consistent results reported by other studies with a similar follow-up period. Ganz et al[7] also showed significant improvements in GERD quality of life with a score of 27 off PPIs and 2 after MSA. They also reported a similar rate of freedom from PPIs, but only achieved esophageal acid normalization in 58%. Similarly, Bonavina et al[11] reported achieving a 50% reduction in GERD-HRQL in 85% at 1.6 years of follow-up with 85% of patients free from PPIs and a pH normalization rate of 67%. In a shorter follow-up interval, Louie et al[12] reported similar improvements in GERD-HRQL and pH normalization of 56% though all patients were off of PPIs. Lastly, 3 studies without objective post MSA pH evaluation, reported freedom from PPIs rates ranging from 81% to 83%.[13–15] Comparatively, Nissen fundoplication results in similar improvements in GERD-HRQL,[15] freedom from PPIs in 63% to 91.5%,[13,14] and postoperative DeMeester scores of 6.1.[16]

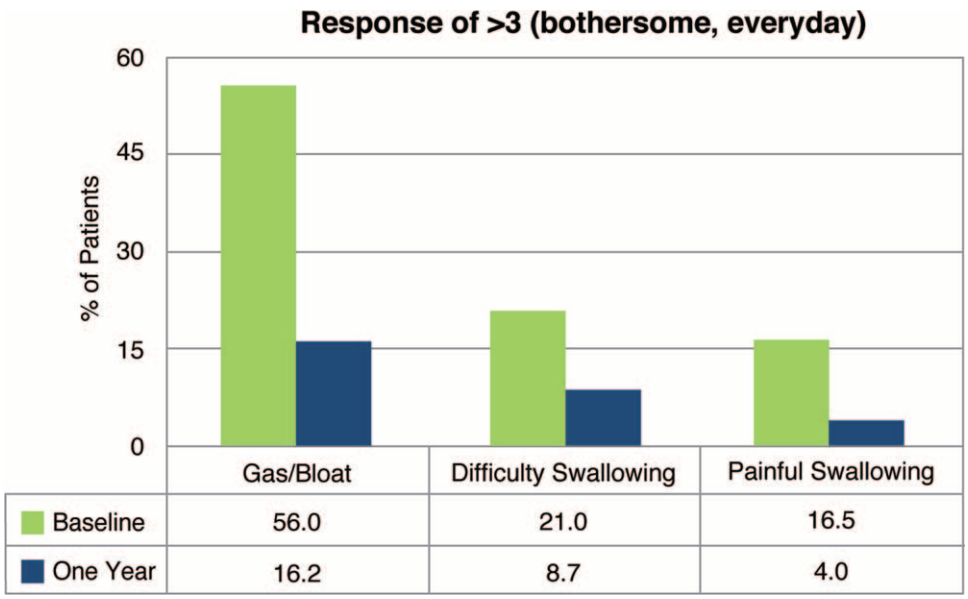

FIGURE 5. Percent of patients reporting symptoms of gas/bloat, difficulty swallowing, and pain with swallowing at baseline and 1 year postimplant based on responses from the GERD-HRQL. GERD-HRQL indicates gastroesophageal reflux disease health-related quality of life.

In multiple studies, MSA has attained remarkably consistent improvements in GERD-HRQL and freedom from PPIs, but the current trial has demonstrated an obvious higher rate of pH control compared with prior studies. This is remarkable because dissemination of technology often sees a reduction in effectiveness once it is used outside the realm of the clinical trial. Several hypotheses may explain this. First, increasing experience with implantation has improved and refined the implantation technique over time. A minimal dissection was recommended during implantation so as to rely on the native structures to maintain placement of the MSA as well as to assist in augmentation. Second, this minimal dissection represents a departure for most antireflux surgeons and it is possible that more dissection and crural repair occurred during this trial since it has more recently been recognized that restoring sphincter characteristics and hiatal closure may influence MSA outcomes.[17]

The ability of magnetic sphincter augmentation to restore a functional and physiologic reflux barrier is unique among antireflux therapies. Medical therapies are directed at altering the acidity of the gastric reservoir toward a more alkaline state in hopes of resolving symptoms and ignore the role of the lower esophageal sphincter and the reflux barrier.[18] In contrast, Nissen fundoplication will restore a functional reflux barrier, but it functions more like a 1-way valve. This provides supranormal reflux control but limits the ability to belch or vomit.[12] Manometric studies have also demonstrated that implantation of a MSA device does augment or restore native valve characteristics and that the restored valve does recreate the physiologic barrier allowing patients to maintain the ability to belch and vomit, particularly when compared with Nissen fundoplication.[13,15,17]

Because the recreated valve after MSA is conceptually a 2-way valve—allowing eructation to occur but also maintaining a barrier to refluxed gastric juice, there is the possibility that some patients will still experience some reflux. This is evidenced by the fact that 12% to 15% of patients require PPIs but less than 10% require daily PPIs suggesting that these patients have still benefitted from magnetic sphincter augmentation by reducing their PPI requirements. Even though symptomatic patients may require intermittent PPI or H2 blockers to control burning symptoms, the regurgitation component of the symptoms is much better controlled with restoration of the reflux barrier. We do not view this as a failure of magnetic sphincter augmentation because if patients can reduce their dependence on PPIs, by having their symptoms controlled while maintaining a physiologic barrier, this becomes a potent antireflux strategy for physicians managing GERD patients.

The most common side effect described by patients after magnetic sphincter augmentation remains dysphagia, which occurs in 2 distinct patterns. The first is during the immediate postoperative period and is fairly predictable in time course and resolution since it closely matches the time period of scarring and encapsulation of the device. Although this is universally well tolerated there is some individual variability in regards to both duration and intensity. The biggest success factor in the management of this has been the clinician and patient understanding and preprocedural expectation setting regarding this process. Encouraging patients to have frequent small meals and avoiding a liquid only diet has helped maintain the ability to tolerate a diet through this early period of dysphagia. It has been rare that a true intervention such as dilation has been required to address this dysphagia. Early in the clinical experience there was a tendency to want to take action through dilation, which potentially could have extended and increased the inflammatory process.[19] For patients whose dysphagia is not well managed through counseling and diet, current experience suggests that a short course of steroids to reduce inflammation and swelling and allow for the natural healing process to run its course prior to the consideration of dilation.

The second pattern for dysphagia, which is much less common, does not appear to follow the expected time course described above. These patients have more significant symptoms that may include repeated vomiting, severe chest pain, and food impaction. In these uncommon instances, these patients may have developed secondary spastic motility disturbances leading to chest pain. Alternatively, albeit rare, they may develop pseudoachalasia simply from implantation of the device. Manometry is often helpful in these situations. These situations have also been reported after fundoplication[20,21] and lap band implantation.[22–25] Lastly, the development of new onset dysphagia or worsening dysphagia after a period of stability warrants further investigation particularly upper endoscopy and/or barium swallow to evaluate for the potential for erosion or mediastinal herniation.

The overall rate of device explantation was 2.5% (5/200) in this series. This is consistent with Ganz et al[7] who reported a 4% rate of explantation for similar symptoms and with Lipham et al[26] who reported 3.4% removal rate in the first 1000 devices implanted worldwide. Comparatively, this rate is significantly lower than other devices implanted around the gastroesophageal junction such as a lap band which is estimated to undergo removal over 10% of the time[27] or the Angelchik device which underwent revision nearly 20% of the time.[28] While this explantation rate may seem higher than expected, part of the attraction is the ''reversibility'' of the procedure which is usually simple to perform and far easier than undoing a fundoplication. Moreover, it usually results in a return to baseline or better for the patient if removed.

There are several limitations to this study. First, there is no comparison group but this post FDA approval study was designed with FDA input and approval as a single arm study. Nevertheless, comparisons can be drawn upon the common outcomes such as GERD-HRQL and objective pH data since these outcomes are used in many studies. The magnitude of the quality of life improvements may vary in studies depending on whether the baseline evaluation was on or off medical therapy. Second, results have only been presented for the first year of a planned 5-year follow-up study. Lastly, it is possible that these results are not generalizable since the investigators are all from high volume esophageal centers, though there is a mixture of academic and community practices.

CONCLUSION

The results from this Post Approval Study at 1 year further confirm magnetic sphincter augmentation as a safe and effective option for patients desiring a surgical option other than fundoplication to control their chronic symptoms of GERD. The reproducibility, high degree of safety, and successful outcomes achieved with the magnetic sphincter augmentation suggest this modality could be considered a primary treatment option in patients with mild GERD.

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