

Magnetic Augmentation of the Lower Esophageal Sphincter: Results of a Feasibility Clinical Trial

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Abstract

Background The high prevalence of gastroesophageal reflux disease continues to encourage the development of treatment modalities to fill the gap between acid-suppression therapy and the laparoscopic Nissen fundoplication. The Magnetic Sphincter Augmentation device has been designed to augment the lower esophageal sphincter barrier using magnetic force. A multi-center feasibility trial was done to evaluate safety and efficacy.

Methods Patients with typical heartburn (at least partially responding to proton-pump inhibitors), abnormal esophageal acid exposure, and normal esophageal peristalsis were enrolled. Patients with hiatal hernia >3 cm were excluded from the study. The device was implanted laparoscopically around the distal esophagus.

Results Over a 1-year period, 38 out of 41 enrolled patients underwent this procedure in 3 hospitals. No operative complications were recorded. A free diet was allowed since post-operative day one, and 97% of patients were discharged within 48 h. The mean follow-up was 209 days (range 12–434 days). The GERD-HRQL score decreased from 26.0 to 1.0 ($p < 0.005$). At 3 months post-operatively, 89% of patients were off anti-reflux medications, and 79% of patients had a normal 24-h pH test. All patients preserved the ability to belch. Mild dysphagia occurred in 45% of patients. No migrations or erosions of the device occurred.

Conclusions Laparoscopic implant of the MSA device is safe and well tolerated. It requires minimal surgical dissection and a short learning curve compared to the conventional Nissen fundoplication.

Keywords Gastroesophageal reflux disease · Lower esophageal sphincter · Laparoscopic Nissen fundoplication · Phrenoesophageal ligament · Proton pump inhibitors

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The incidence of gastroesophageal reflux disease (GERD) is increasing along with its complications of Barrett's esophagus and adenocarcinoma.^{1–3} This has occurred despite the widespread use of potent acid-suppression therapy, namely the proton-pump inhibitors (PPI). Further, patients on maximum dose PPI therapy may complain of persistent regurgitation or may develop atypical GERD symptoms. The inability of pharmacologic therapy to limit the progression of the disease or to fully suppress all symptoms has encouraged many patients to have anti-reflux surgery, most commonly the Nissen fundoplication. The Nissen procedure, however, is technically complex, it results in major alteration of gastric anatomy, and has variable outcomes from center to center. Consequently, it tends to be applied primarily to patients with advanced reflux disease as an end of the line therapy.

To fill the treatment gap between acid-suppression therapy and the Nissen fundoplication, a variety of endoluminal anti-reflux procedures have emerged. These

endoluminal procedures were primarily designed for use in patients with relatively normal anatomy of the esophago-gastric junction (small or no hiatal hernia) and incomplete symptom resolution or non compliance with PPI therapy. Unfortunately, these endoluminal procedures have yet to show consistent normalization of distal esophageal acid exposure as defined by 24-h pH monitoring. Published studies show a pH normalization range of only 25–40%.^{4,5} Consequently, a need still exists for a therapy to fill the gap between pharmacologic therapy and the Nissen fundoplication. The Magnetic Sphincter Augmentation (MSA) device was developed to meet this need. The MSA is a laparoscopically implantable device that is designed to restore Lower Esophageal Sphincter (LES) barrier function using magnetic force. The device requires minimal surgical dissection, maintains normal gastroesophageal junction and gastric anatomy, and is designed to preserve physiologic functions such as belch and vomiting. The treatment is currently intended for patients who fail medical therapy but have otherwise normal anatomy of the esophago-gastric junction.

The MSA device consists of a series of titanium beads with a magnetic core (Fig. 1). The beads are linked together with independent titanium arms to form a flexible ring that is placed around the distal esophagus. The magnetic attraction of the beads provides a sustained force to augment the LES barrier. The device expands to accommodate a swallowed bolus, and the magnetic force between the beads is exponentially reduced with distension of the sphincter. A multi-center, feasibility trial was done to evaluate the MSA device.

Methods

Trial Objective and Design

The objectives of this prospective, feasibility trial were to: (1) demonstrate the safety of the MSA device; (2) measure the effectiveness of the device in reducing esophageal acid exposure; (3) standardize the laparoscopic technique for implantation of the MSA device; (4) evaluate the effects of the device on the LES and esophageal body function; (5) measure the ability of the device to improve GERD related symptoms and quality of life; (6) measure the ability of the device to reduce GERD related medication use; (7) determine any potential side-effect caused by the device.

Patient inclusion criteria were: typical reflux symptoms at least partially responsive to PPI, abnormal esophageal acid exposure, and normal contraction amplitude and wave form in the esophageal body. Patients exclusion criteria were: younger than 18 and older than 75 years of age, previous upper abdominal surgery, previous endoscopic anti-reflux procedures, greater than 3 cm sliding hiatal hernia, greater than grade A esophagitis according to the Los Angeles classification, and/or the presence of Barrett's esophagus on endoscopic biopsies. The trial design is depicted in Fig. 2.

The study protocol was approved by the Ethical Committee of the IRCCS Policlinico San Donato, University of Milan, Milan, Italy, and the Institutional Review Boards of the Chapman Medical Center, Orange, CA, USA, and Abbott Northwestern Hospital, Minneapolis, USA. Each patient was informed about the investigational nature of the trial, and received detailed information about the

Figure 1 Engineering schematic of the magnetic sphincter augmentation device open (a) and closed (b). Closed force is 0.40 N and open force is 0.07 N.

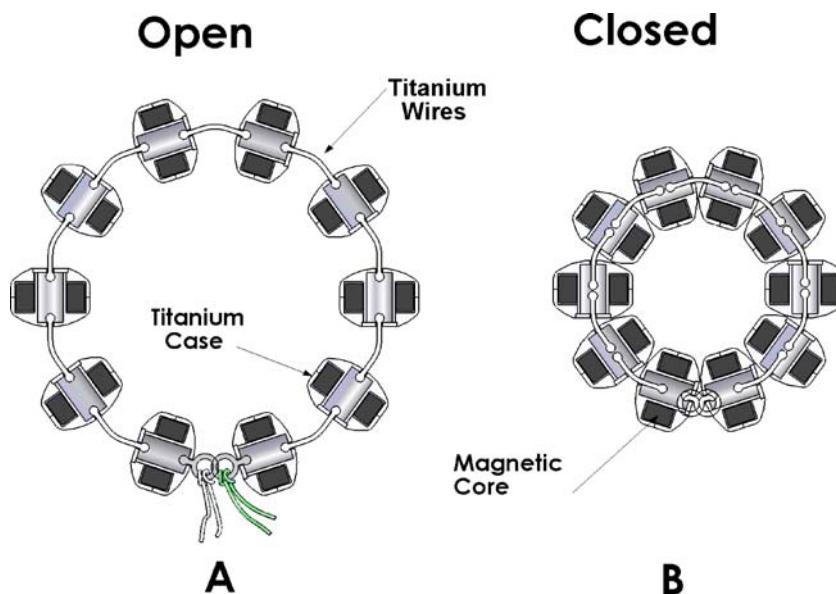


Figure 2 Design of the clinical trial.

Screening	Implant	2 week	6 week.	3 month	6 month	12 month	Type of Follow-Up
X						X	Health History
X		X	X	X	X	X	GERD-HRQL
X	X	X	X	X	X	X	PPI, H2, Antacid Use
X				X		X	24hr pH Profile
X				X		X	Manometry/Motility
X				X		X	Endoscopy
X				X		X	Barium Esophagram (Fluoroscopy)
	X		X	X		X	Abdominal/Chest X-ray
	X	X	X	X	X	X	Adverse Events

study protocol. A written informed consent was obtained before enrollment in the trial.

Study Population and Preoperative Assessment

Between February 26, 2007 and May 20, 2008, 41 patients were enrolled for laparoscopic implantation of the MSA device, were evaluated by symptom questionnaire, upper gastrointestinal endoscopy, barium swallow, esophageal manometry, and 24-h esophageal pH monitoring.

The gastroesophageal reflux disease-Health Related Quality of Life (GERD-HRQL) questionnaire was administered pre-operatively and off PPI therapy to all patients prior to any diagnostic test.⁶ Upper gastrointestinal endoscopy was performed to assess the presence of esophagitis using the Los Angeles classification. The length of hiatal hernia, if present, was measured as the distance in cm between the Z line and the impression of the crura.

Esophageal manometry was performed and LES pressure and length were measured with a station pull-through technique. The degree of LES relaxation was assessed with five monitored swallows. Esophageal contractility was assessed with ten wet swallows (5 ml each, 30 s apart). Abnormal motility was defined as a mean contraction amplitude of 30 mmHg or less, and/or a greater than 20% prevalence of simultaneous waves.

Twenty-four hour pH monitoring was performed off acid-suppression therapy by placing the pH probe or capsule 5 cm above the upper border of the LES determined by manometry or 6 cm above the Z line determined by endoscopy. Abnormal esophageal acid exposure was defined as a DeMeester pH score >14.7.⁷

Implantation of the MSA Device

The MSA device was supplied sterile and was placed through a 10 mm laparoscopic port. The MSA device was available in different lengths, based on the number of beads, to accommodate the varied esophageal circumferences. Sutures were attached to eyelets at each end of the device to secure the implant. A specially designed sizing tool was wrapped around the distal esophagus before placement of the device, so that the surgeon was able to select the appropriate size of implant (Fig. 3).

The device was implanted laparoscopically under general anesthesia with the patient in the lithotomy position. A 11-mm port for the 30° scope was inserted at the lower third of the distance between the xyphoid process and the umbilicus. An all-purpose 12-mm port was placed in the left subcostal area and a 5 mm dissection port in the right subcostal area in the midclavicular line. An additional 5 mm port was placed below the xyphoid process for liver retraction. A 5 mm port was placed in the left flank at the level of the umbilicus for downward traction of the stomach. With the patient in a reverse (20–30°) Trendelenburg position, the subcardial stomach was retracted downward. The peritoneal reflection anterior to the gastroesophageal junction was divided to expose the esophageal wall. The anterior vagal trunk was identified, but no attempt was made to dissect it from its intramuscular location. The hepatic branch of the anterior vagus nerve was preserved. The lesser omentum beneath the nerve was opened to allow a better exposure of the right crus. The retro-esophageal dissection began along the border of the right crus at the lateral aspect of the distal esophagus, just cephalad to the crural decussation. The posterior vagal trunk was identified. The same dissection was repeated along the left crus of the diaphragm. Gentle dissection from the right opened the retro-esophageal

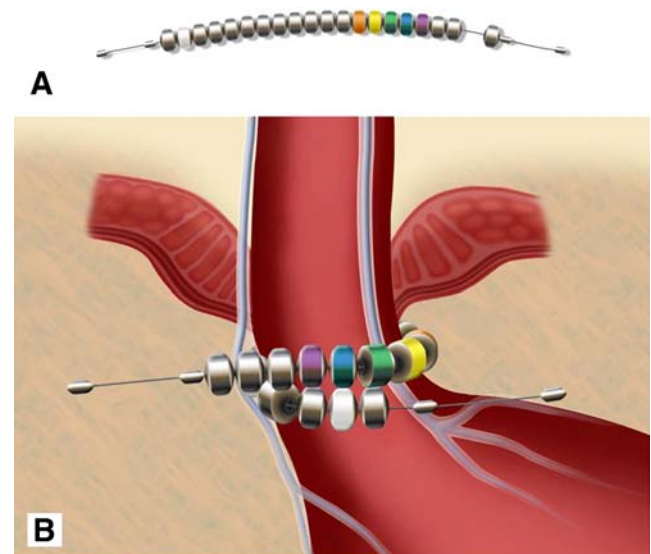


Figure 3 Sizing tool **a** used to fit loosely around distal esophagus **b** to determine the appropriate MSA device for the individual patient.



Figure 4 The MSA device is inserted along a tunnel between the esophageal wall and the posterior vagus nerve.

window between the posterior wall of the esophagus and the posterior vagal trunk (Fig. 4). Continuous downward traction on the gastroesophageal junction and application of 10–15 mmHg of positive-end expiratory pressure helped the dissection. A Penrose drain was passed through the retroesophageal window to encircle the esophagus.

The sizing tool was introduced through the all-purpose trocar, advanced through the posterior esophageal tunnel, and wrapped around the esophagus above the hepatic branch of the anterior vagal trunk. The appropriate size device to be implanted is selected by alignment of the white bead with one of the colored beads (Fig. 3b) The sizing tool was removed and the MSA device inserted. The sutures at both ends of the device were secured with a Ti-Knot® (LSI Solutions, Victor, NY, USA; Fig. 5).

The target location of the MSA device was the Z line. This location can be verified with intraoperative endoscopy

prior to securing the sutures (Fig. 5b). A posterior cruroplasty was added to MSA device placement in five of 38 patients.

Post-operative Assessment

Position and function of the device were evaluated with a standard chest film and a modified barium esophagram the day after the procedure before hospital discharge. The GERD-HRQL questionnaire, upper gastrointestinal endoscopy, modified barium esophagram, esophageal manometry, and 24-h esophageal pH monitoring were obtained at 3 months and 1 year after surgery.

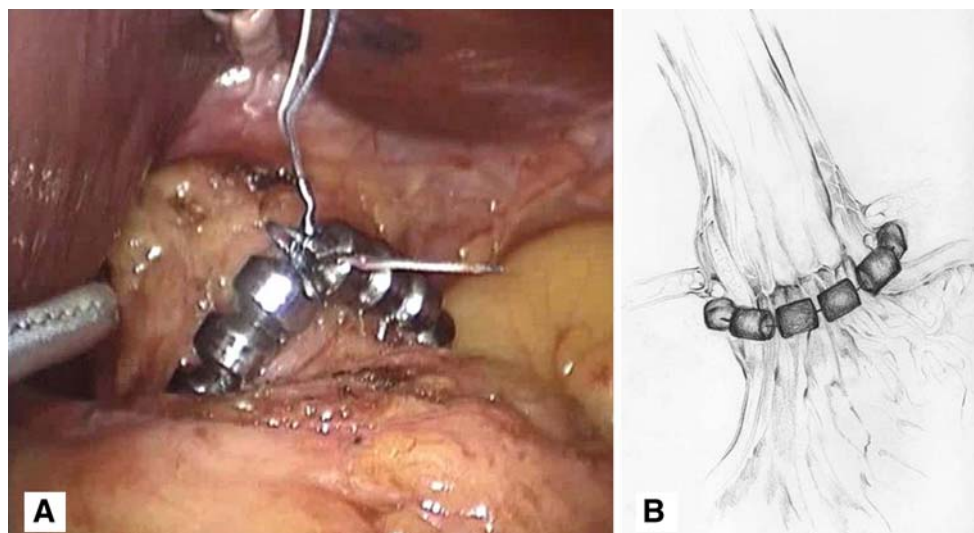
Statistical Analysis

The two-tailed, paired Student *T* test was used to compare pre and post-operative values. Differences were considered significant at the $p < 0.05$ level.

Results

Three of the 41 patients enrolled were not implanted with the MSA device. One was converted to a Nissen fundoplication due to the intraoperative finding of a hiatal hernia >3 cm and a leiomyoma at the esophagogastric junction. A second patient withdrew consent before surgery was scheduled; a third patient was ineligible due to preoperative esophageal motility testing results showing ineffective peristalsis. The final study population was composed of 38 patients, 23 males and 15 females ranging in age from 19 to 72 years (median 42.8). The BMI ranged from 19 to 38.4 (median 24.5). All patients complained of heartburn as the primary symptom and were taking PPI (single or double

Figure 5 Final intraoperative position of the MSA device (a). The target location is the Z line (b).



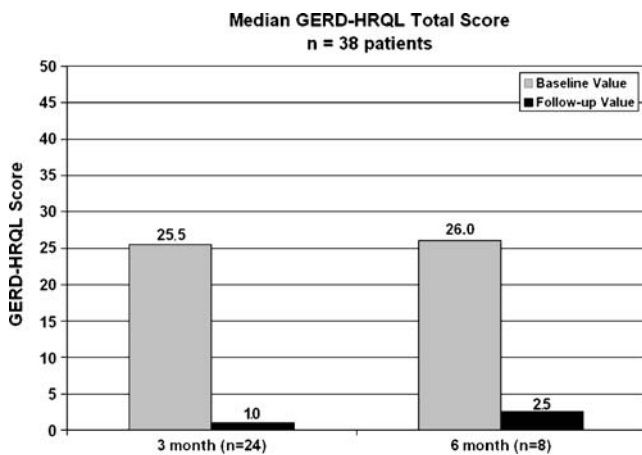


Figure 6 Median GERD-HRQL score before surgery and at various time intervals after surgery.

dose) for acid suppression. A ≤ 3 cm sliding hiatal hernia based on radiologic and/or endoscopic criteria was observed in 60.5% (23/38) of the patients. All patients had an abnormal DeMeester pH score that ranged from 15.1 to 117.3 (median 31.4) after being off acid suppression therapy for a minimum of 10 days.

Post-operative Course

All devices were implanted by the laparoscopic approach without operative complication. The median operative time was 40 min. A regular diet was allowed after radiological assessment of esophageal transit on the first post-operative. All but one patient (37/38) 97% were discharged within 48 h.

Therapeutic Response

As of May 20, 2008 the mean follow-up was 209 days (range 12–434 days). Eighty-nine percent of the patients

were off PPI at 3 months. Mild dysphagia occurred in 17 patients (45%) and resolved in the majority without any treatment. One patient required laparoscopic removal eight months after implantation for persistent dysphagia and pathologic esophageal acid exposure on 24-h pH test. The revisional procedure was uneventful, and dysphagia resolved. The median GERD-HRQL score decreased from 26.0 pre-operatively to 1.0 at 3 months and 2.5 at 6 months ($p < 0.005$ for both time points) (Fig. 6). A post-hoc questionnaire was completed by all 38 patients. All reported the ability to belch and, four, the ability to vomit after insertion of the device

Barium Swallow

In 36 of 38 patients the MSA device was observed immediately below the diaphragm (Fig. 7) and in two, 1–2 cm above the diaphragm. Both of the latter patients had a < 3 cm hiatal hernia pre-operatively that was not repaired during placement of the device. Both patients normalized their distal acid exposure. No device migration occurred.

Endoscopy

No mucosal breaks occurred. Upper gastrointestinal endoscopy was performed in 24 patients that completed a 3-month follow-up. At endoscopy, the device was 0.5–2.0 cm below the Z line in 19 patients, at the Z line in three, and greater than 2 cm below the Z line in two. Both of the latter patients had pathologic esophageal acid exposure at 3 months testing.

Esophageal Manometry

There were no significant changes in the manometric parameters after MSA implantation compared to pre-surgical manometric data as reported in Table 1.

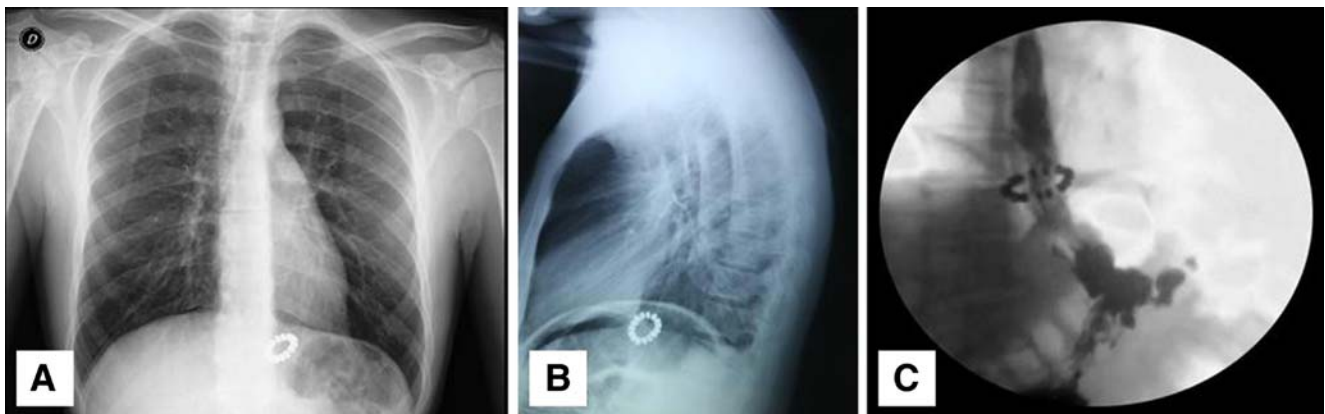


Figure 7 Radiological appearance of the MSA device on AP chest film (a), lateral chest film (b), and barium esophagram (c).

Table 1 Results of Esophageal Manometry Before and After Laparoscopic Implantation of the Magnetic Sphincter Augmentation (MSA) device

	Baseline n=37	Pre n=18	Post n=18	p value
Mean LES resting tone (mmHg)	13.9	14.1	16.0	0.19
Mean LES length (cm)	4.5	4.4	5.3	0.15
Mean LES abdominal length (cm)	2.7	2.7	3.6	0.11
Mean LES relaxation (%)	97	97	98	0.96
Mean swallows effective (%)	96	96	99	0.17

24-hour Esophageal pH Monitoring

Overall, 19/24 (79.2%) patients returned to normal esophageal acid exposure at 3 months. Comparison of the pre- and post-operative pH parameters are reported in Figs. 8 and 9, and in Table 2.

Discussion

Continuous PPI therapy is the first line approach in patients with GERD. However, for a percentage of patients this treatment is insufficient due to incomplete relief of heartburn, persistent regurgitation, drug side-effects, the emergence of atypical symptoms, a desire not to be dependent on life-long pharmacological therapy, and progression of the disease to Barrett’s esophagus and adenocarcinoma during treatment. The cumulative effects of these limitations lead many patients with GERD to consider surgical therapy. At present, this is a laparoscopic Nissen fundoplication. It is generally acknowledged that the laparoscopic Nissen fundoplication is a very effective and durable operation when performed in specialized centers.⁸⁻¹² However, the success rate varies widely.¹³ Reports from the

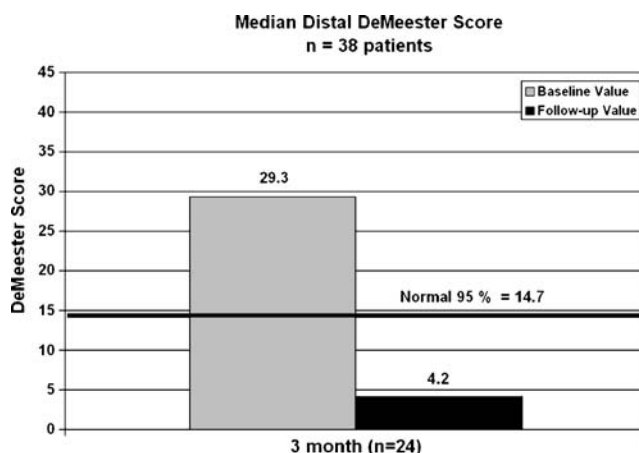


Figure 9 Median composite DeMeester score before and after surgery.

community on Nissen fundoplication outcomes show that only 61% of patients were satisfied with the procedure and 32% were still taking medications on a regular basis for heartburn.¹⁴ This is likely the reason for the reported 30% decrease in the number of anti-reflux operations performed in the USA between 2000 and 2003.¹⁵ The intent of the MSA device is to provide a more simple and standardized minimally invasive surgical therapy for patients with GERD who are dissatisfied with their current medical therapy.

We recognize that a foreign body placed near the gastroesophageal junction can be at risk for erosion into the esophageal lumen. The MSA device has been designed specifically to reduce or eliminate the propensity for erosion. It is nonrestrictive with regard to esophageal motion or distension. The volume of the MSA device is 2 ml or less. This is markedly less than the approximate 50 ml volume of the Angelchik prosthesis and, consequently, the displacement pressure on adjacent tissue is less. Further, at rest, the MSA device is designed to encircle the esophagus in the form of a “Roman arch” to avoid compression of the tubular esophagus. These design features allow the MSA device to work in harmony with the esophagus and lessen the propensity for erosion. In a

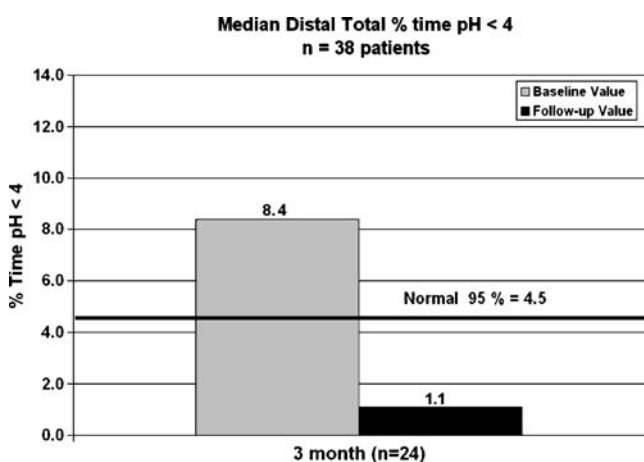


Figure 8 Median distal esophageal acid exposure (% time pH<4) before and after surgery.

Table 2 Results of 24-h Esophageal pH Monitoring Before and After Laparoscopic Implantation of the Magnetic Sphincter Augmentation (MSA) device

	Baseline n=38	Pre n=24	Post n=24	p value
DeMeester score	31.4	29.3	4.2	<0.001
Total % time <pH 4	9.8	8.4	1.1	<0.001
Upright % time <pH 4	10.9	10.6	1.3	<0.001
Supine % time <pH 4	5.0	3.3	0.1	<0.01
No. of episodes	66	67	12	<0.001
No. of episodes >5 min	5.5	5	1	<0.001
Longest episode (min)	31	28	5	<0.04

porcine model, LES augmentation with the MSA device allowed normal eating behavior and weight gain without alteration of tissue histology or erosion of the device.¹⁶

A legitimate question is why develop a new anti-reflux procedure when a laparoscopic Nissen fundoplication currently exists and has a reputed good outcome. The Nissen fundoplication, when done correctly is technically complex and results in significant alteration of gastric anatomy. Consequently, it has inconsistent outcomes and a potential for side-effects.¹⁴ This outweighs the benefits for patients with early disease. The ability to perform a simpler and more standardized antireflux procedures in the outpatient setting would make the procedure more acceptable to patients and physicians. At present, the Nissen fundoplication is rarely performed as an outpatient procedure. In contrast, the MSA device is suited for insertion in the outpatient setting. Further, the implantation of the MSA device is expected to be simpler and more standardized, resulting in less outcome variability. We agree that the Nissen fundoplication has a proven track record for patients with advanced GERD and the efficacy of the MSA device for these patients remains to be determined. At present, the MSA device is targeted to fill the treatment gap between patients with failed acid-suppression therapy and those with advanced disease that require a Nissen fundoplication.

This study shows that the implantation of the MSA device requires minimal surgical dissection, thereby preserving the normal anatomy of the stomach and esophagogastric junction. In most patients, a distinct phrenoesophageal ligament was identified and care was taken to preserve the upper leaf of this structure which fuses with the esophageal adventitia.¹⁷ Preservation of the phrenoesophageal ligament, combined with the exclusion of the posterior vagus nerve, is likely to provide a safe anchoring of the MSA device around the LES and to prevent proximal migration. Based on design and supporting in vitro and in vivo testing,¹⁶ the device increases the pressure required to open the LES by interrupting distraction of the sphincter by gastric wall tension. In other words, the magnetic force of the MSA device, which is highest when the device is closed, prevents the LES shortening induced by gastric distension.^{18,19} Interestingly, all patients queried in this series were able to belch after surgery. As expected, post-operative manometric values at rest did not change compared to preoperative findings.

This initial clinical experience suggests that laparoscopic placement of the MSA device is a safe and reproducible method of augmenting the LES while preserving the ability to belch and vomit. It has the additional advantage of being a reversible procedure.²⁰ The MSA device produced consistent symptomatic improvement in all patients and pH normalization in 80% of patients. Further clinical and objective follow-up are underway and an additional trial

has been planned to further assess the safety and effectiveness of magnetic sphincter augmentation.

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