Laparoscopic Sphincter Augmentation Device Eliminates Reflux Symptoms and Normalizes Esophageal Acid Exposure: One and Two Year Results of a Feasibility Trial

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MINI ABSTRACT
Laparoscopic sphincter augmentation device proved effective for control of symptoms and normalization of esophageal acid exposure at one and two years of follow-up. Standardized insertion technique, preservation of normal anatomy, consistent outcomes and minimal side effects are the main features of this surgical procedure.
**ABSTRACT**

**Objectives**

One and two year evaluation of a feasibility trial (clinicaltrials.gov registration numbers NCT01057992, NCT01058070, and 01058564) to assess the safety and efficacy of a laparoscopically implanted sphincter augmentation device for the treatment of gastroesophageal reflux disease (GERD).

**Methods**

A sphincter augmentation device (LINX™ Reflux Management System, Torax Medical, Shoreview, MN, USA), designed to prevent reflux due to abnormal opening of the lower esophageal sphincter (LES), was laparoscopically implanted at the gastro-esophageal junction (GEJ) in 44 patients. At baseline all patients had abnormal esophageal acid exposure on 24-hour pH monitoring and improved, but persistent, typical GERD symptoms while on acid suppression therapy with proton pump inhibitors (PPI). The device comprises a miniature string of interlinked titanium beads, with magnetic cores, placed around the GEJ. The magnetic bond between adjacent beads augments sphincter competence. The beads temporarily separate to accommodate a swallowed bolus, allow belching or vomiting, and re-approximate to augment the LES in the closed position. Patients were evaluated after surgery by GERD-HRQL symptom score, PPI usage, endoscopy, esophageal manometry, and 24-hour esophageal pH monitoring.

**Results**

The total mean GERD-HRQL symptom scores improved from a mean baseline value of 25.7 to 3.8 and 2.4 at one and two year follow-up, representing an 85% and 90% reduction, respectively (p<.0001). Complete cessation of PPI use was reported by 90% of patients at one year and by 86% of patients at two years. Early dysphagia occurred in 43% of the patients and self-resolved by 90 days. One device was laparoscopically explanted for persistent dysphagia without disruption of the anatomy or function of the cardia. There were no device migrations, erosions or induced mucosal injuries. At one and two years, 77% and 90% of patients had a normal esophageal acid exposure. The mean percent time pH was <4 decreased from a baseline of 11.9% to 3.1% (p<.0001) at one year, and to 2.4% (p<.0001) at 2 years. Patient satisfaction was 87% at 1 year and 86% at 2 years.

**Conclusions**

The new laparoscopically implanted sphincter augmentation device eliminates GERD symptoms without creating undo side effects, and is effective at one and two years of follow-up.

**Keywords:** gastroesophageal reflux disease, Barrett’s esophagus, esophageal adenocarcinoma, lower esophageal sphincter, gastroesophageal junction, proton-pump inhibitors, laparoscopic Nissen fundoplication

**INTRODUCTION**

Gastroesophageal reflux disease (GERD) is a common disorder of the alimentary tract. The disease affects at least 10% of the population in western countries and is the leading physician diagnosis in gastroenterology outpatient clinics. Acid suppression with proton-pump inhibitors (PPI) is the first-line therapy, but in almost 40% of patients, GERD-related symptoms persist despite high-dose medication (1-3). Further, it has been shown that patients with a mechanically defective lower esophageal sphincter (LES) are particularly difficult to maintain in a symptom-free state. They have nocturnal acid breakthrough, non-acid reflux and can progress to complications of the disease, such as position-related regurgitation with aspiration and Barrett’s metaplasia (4, 5). These limitations of acid suppression therapy have encouraged the search for a more effective treatment by augmenting the lower esophageal sphincter (LES), rather than only depending on continuous suppression of gastric acid secretion (6).

The laparoscopic Nissen fundoplication can be used to treat these patients and is generally acknowledged to be an effective and durable therapy when performed by expert surgeons in specialized centers (7). However, outside of such centers the success rate varies widely (8). Patients who have a Nissen operation are expected to accept a trade-off between relief of GERD symptoms and the potential side effects of the procedure, namely the inability to belch and vomit and the possibility of chronic dysphagia (9). Consequently, gastroenterologists tend to limit their referrals for the Nissen procedure to patients with large hiatal hernia or advanced GERD.

The current treatment algorithm leaves a therapeutic gap of dissatisfied patients between those who are satisfied with their acid suppression therapy and those who had a Nissen fundoplication for advanced disease. The question emerges as to what is the best treatment for these “gap patients” who are dissatisfied with acid suppression therapy, but remain reluctant to have a Nissen fundoplication due to concerns over the side effects of the procedure.

The LINX device was developed to address this “therapy gap” with a simple standardized laparoscopic procedure that does not alter the anatomy of the cardia, provides relief of reflux-related symptoms without impeding the ability to belch or vomit, and is reversible if necessary. Importantly, the operation can be performed safely by surgeons using standard laparoscopic techniques and instruments.
The intent of the LINX device is to augment the barrier function of the LES. For reflux to occur through an augmented LES, gastric pressures must overcome both the patient’s native LES pressure and the magnetic bonds of the device. Importantly, the device, while augmenting the LES, also expands to accommodate a swallowed bolus and allows belching or vomiting if needed. After laboratory testing in animals (10), the device was approved for a clinical feasibility study in humans. The aim of this paper is to report the one and two year results of this new device for the treatment of GERD.

**METHODS**

**Study design**

A multi-center, prospective clinical study was performed to evaluate the safety and efficacy of the LINX device in a cohort of patients with GERD. The short-term results of this trial have already been reported (11). The study protocol was approved by the Ethical Committee or Institutional Review Board of the participating institutions. The trial was registered with clinicaltrials.gov (NCT01057992, NCT01058070, and 01058564). Each patient was informed about the investigational nature of the trial, and received detailed information about the study protocol. A written informed consent was obtained before enrollment in the trial. The objectives of the present report were to evaluate the safety and efficacy of the device in humans after one and two years of implantation.

Patient inclusion criteria were: age >18 and < 85 years, typical reflux symptoms at least partially responsive to PPI therapy, abnormal esophageal acid exposure, and normal contraction amplitude and waveform in the esophageal body. Patients exclusion criteria were: symptoms of dysphagia, previous upper abdominal surgery, previous endoluminal antireflux procedures, >3 cm sliding hiatal hernia, greater than grade A esophagitis, and/or the presence of histologically documented Barrett’s esophagus.

**Patient population**

A total of 44 patients had laparoscopic implantation of the LINX device between February 2007 and October 2008. There were 26 (59%) males and 18 (41%) females, mean age 42.3 yrs, range 19-72 years. The BMI ranged from 19.0 to 38.4 (mean 25.7). Heartburn was the primary symptom in all patients and all were taking proton-pump inhibitors at standard or double dose for acid suppression. Eighteen patients had no hernia and twenty-six of the 44 patients (59.1%) had a <3cm sliding hiatal hernia based on radiologic and/or endoscopic criteria.

**Preoperative assessment**

Each patient was evaluated before surgery with a symptom questionnaire, upper gastrointestinal endoscopy, barium swallow, esophageal manometry, and 24-hour esophageal pH monitoring. The Gastro-Esophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) questionnaire (12) was administered preoperatively off PPI therapy, prior to any diagnostic test. This validated questionnaire consists of six heartburn related questions, two swallow related questions, one gas bloat question and one question related to medication use. The responses to these questions are scored according to definitions in TABLE 1.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms noticeable but not bothersome</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms noticeable and bothersome but not every day</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms bothersome every day</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms affect daily activities</td>
</tr>
<tr>
<td>5</td>
<td>Symptoms are incapacitating – unable to do activities</td>
</tr>
</tbody>
</table>

**TABLE 1 – Scoring scale of the GERD-HRQL questionnaire**

Upper gastrointestinal endoscopy was performed to assess the presence of esophagitis using the Los Angeles or Savary-Miller classification. The length of hiatal hernia, if present, was measured as the distance between the gastroesophageal junction (GEJ), defined by the proximal limit of the gastric folds, and the crural impression.

Esophageal manometry was used to measure LES pressure and length with a station pull-through technique. The degree of LES relaxation was assessed with five wet swallows. Esophageal contractility was assessed by ten wet swallows of 5 ml each, taken 30 seconds apart. Abnormal motility was defined as mean contraction amplitude of 30 mmHg or less, and/or a greater than 30% prevalence of simultaneous, dropped or interrupted waves.

Twenty-four hour esophageal pH monitoring was performed off PPI therapy by placing the pH probe or capsule 5cm 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 verified prior to implant.
Features of the sphincter augmentation device

The LINX device consists of a series of titanium beads with magnetic cores hermetically sealed inside. The beads are interlinked together with independent titanium wires to form a flexible ring that rests around the LES in a circular fashion (FIGURE 1a). The strength of the magnetic core contained in each bead is designed by mass to augment the sphincter’s ability to resist opening from gastric pressures. The augmentation force provided by the device is permanent. When implanted all the beads are touching each other to insure no compression of the esophageal wall (FIGURE 1b). The magnetic bond between beads is easily broken by the transport force of a swallowed bolus, allowing the beads to separate and a food bolus to freely pass (FIGURE 1c). The attraction force between magnets exponentially reduces with the separation distance. The device is capable of nearly doubling its diameter when all beads are separated. Unique to the design is that the magnetic attraction force that must be overcome to allow separation of the beads is the same regardless of the number of beads contained in the device (FIGURE 2).

The device is manufactured in different lengths based on the number of beads necessary to accommodate the varied esophageal circumferences. The smallest and the largest configuration consist of 10 to 18 beads. Before implantation the device is sized specifically to the circumference of the patient’s esophagus using a special measuring tool that is wrapped around the esophagus at the GEJ to select the appropriate size of the implant (FIGURE 3).
Surgical technique
The device is implanted laparoscopically under general anesthesia. The visceral peritoneum on the anterior surface of the esophagogastric junction is divided to expose the anterior esophageal wall. The anterior vagal trunk is identified, but no attempt is made to dissect it from its intramuscular location. The hepatic branch of the anterior vagus nerve is preserved (FIGURE 4a). The retro-esophageal dissection begins along the anterior border of the right crus just cephalad to decussation of the crura. The posterior vagal trunk is identified (FIGURE 4b). The same dissection is repeated along the left crus of the diaphragm. Gentle dissection from the right opens the retro-esophageal window and a tunnel is made between the posterior esophageal wall and the posterior vagal trunk. A 6 mm Penrose drain is passed through the retro-esophageal window to encircle the esophagus. The sizing tool is passed through the posterior esophageal tunnel, and wrapped around the esophagus above the hepatic branch of the anterior vagal trunk. The appropriate size of the LINX device is passed through the tunnel, wrapped around the esophagus proximal to the hepatic branch of the anterior vagus nerve, and laid in the incision made in the visceral peritoneum over the anterior surface of the gastroesophageal junction. The sutures at both ends of the device are secured with a Ti-Knot ® (LSI Solutions, Victor, NY, USA). The target location of the device is the endoscopic Z line. A posterior cruroplasty was added to the procedure in 5 patients.

Postoperative assessment
Initial position and function of the device was verified with a standard chest film and a modified barium esophagram obtained the day after implantation before hospital discharge. The GERD-HRQL questionnaire, upper gastrointestinal endoscopy, modified barium esophagram, and 24-hour esophageal pH monitoring were obtained at three months and at one and two year after surgery. Esophageal manometry was obtained at three months and one year.

Statistical analysis
The two-tailed, paired Student T test was used to compare pre- and postoperative values. Differences were considered significant at the p<0.05 level.

RESULTS
All devices were implanted laparoscopically without operative complications. The median operative time was 40 minutes (range 19-104). A free diet was allowed after radiological assessment of esophageal transit on post-operative day 1. All but one patient was discharged within 48 hours. Mild dysphagia was present in 43% of patients during the postoperative period, and resolved by 90 days without treatment.

The median number of days since implantation was 895 days (range 226 – 1144). To date, 40 of the 44 implanted patients have completed their clinical and pHmetry assessment at either 1 year or 2 year pH follow-up. Two patients were explanted, one at 8 months due to persistent dysphagia, and the other at 18 months due to the need for a MRI study. Two patients withdrew consent, and one subject is lost to follow-up.
Clinical Evaluation

The mean GERD-HRQL score at one year, when compared to the baseline score, decreased by 85%, and at 2 years by 90% (p<.0001) (FIGURE 5). Changes in the specific components of the GERD-HRQL score are shown in TABLE 2. At one and two years 90% and 86% of the patients were completely off PPI therapy. A post-hoc questionnaire showed that all patients maintained their ability to belch; in addition, 4 patients experienced the need to vomit and were able to do so.

Barium swallow

The day after surgery the device was seen positioned just below the diaphragm in 42 patients and 1-2 cm above the diaphragm in two. Both of these patients had a <3 cm hiatus hernia prior to surgery that was not repaired. It is likely that the device in both patients was within the hernia sac. No device migration occurred during the follow-up period.

Endoscopy

On upper gastrointestinal endoscopy the impression of the device was observed in the region of the GEJ in all patients. There was no increased resistance to passage of a standard 9mm endoscope. To date, no mucosal or transmural erosions of the device have been reported.

Esophageal Manometry

Thirty-two patients had both baseline and one-year postoperative manometric testing available for comparison. LES resting pressure increased from 6.5 mmHg to 14.6 mmHg (p<.005) in the 9 patients with a hypotensive (less than 10 mmHg) LES pressure. In the 23 patients with normal LES pressure at baseline, no significant changes in pressure occurred (baseline=18.1 mmHg, postoperative=19.7 mmHg). There were no statistically significant changes in the overall or abdominal length of the LES. Similarly, there were no statistically significant changes in the amplitude of esophageal contractions.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Implant (n=44)</th>
<th>3-month (n=37)</th>
<th>1-year (n=39)</th>
<th>2-year (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How bad is your heartburn?</td>
<td>3.7</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Heartburn when lying down?</td>
<td>3.1</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Heartburn when standing up?</td>
<td>3.3</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Heartburn after meals?</td>
<td>3.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Does heartburn change your diet?</td>
<td>3.1</td>
<td>0.5</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Does heartburn wake you from sleep?</td>
<td>2.5</td>
<td>0.0</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Do you have difficulty swallowing?</td>
<td>1.2</td>
<td>0.7</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Do you have bloating and gassy feelings?</td>
<td>2.9</td>
<td>0.8</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Do you have pain with swallowing?</td>
<td>0.6</td>
<td>0.4</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>If you take medication, does this affect your daily life?</td>
<td>2.0</td>
<td>0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>How satisfied are you with your present condition?*</td>
<td>0%</td>
<td>84%</td>
<td>87%</td>
<td>86%</td>
</tr>
</tbody>
</table>

TABLE 2 - Mean pre-and postoperative scores from GERD-HRQL questionnaire (*% satisfied patients)
24-hour esophageal pH monitoring

The esophageal acid exposure was normalized for the total time in 77% and 90% of patients at 1 and 2 years, respectively (FIGURE 6). The mean % time pH was <4 decreased from a pre-operative baseline of 11.9% to 3.1% at 1 year and 2.4% at 2 years. All the other components of the 24-hour pH test and the DeMeester composite score were significantly reduced compared to baseline at one and two years (TABLE 3).

**DISCUSSION**

The present study shows that augmentation of the LES barrier using the LINX device appears to be an effective minimally invasive therapy for patients with uncomplicated GERD. More than 50 years ago Rudolf Nissen introduced the Nissen fundoplication. Today, the procedure can be performed successfully by laparoscopy. Despite this, its use has been resisted by gastroenterologists because of the variability in outcomes, the risks of new side effects and the degree of anatomical distortion associated with the operation. These limitations are also of concern to patients with uncomplicated disease who are dissatisfied with the relief they obtain from acid suppression therapy. For the most advanced GERD patients, the benefits of the Nissen procedure generally outweigh its side effects.

Partial fundoplication procedures have been proposed as suitable alternatives to reduce the side-effects of the Nissen operation, but this concept has not been proven in randomized clinical trials. Existing literature from experienced centers does not clearly confirm a significant reduction of side-effects while maintaining objective evidence of reflux control (13,14). The LINX device was developed to provide a less variable procedure with a better trade-off between clinical effectiveness and the potential side effects. It was designed specifically for patients with uncomplicated disease who are dissatisfied with their acid suppression therapy.

Migration and erosion of the device has not occurred to date. It is likely that the miniature size of the LINX, its “Roman arch” design and its dynamic properties allow it to mimic the physiologic motion of the esophageal wall, thereby minimizing the likelihood of tissue injury or erosion. Long-term evaluation is needed to confirm this theory. Currently, magnetic resonance imaging (MRI) is contraindicated following LINX. Further testing is planned to evaluate the interaction between the LINX and MRI.

Implantation of the LINX requires minimal surgical dissection with preservation of normal anatomy. In most patients, a distinct phrenoesophageal ligament was identified and preserved (15). This, combined with forming a tunnel between the posterior wall of the esophagus and the posterior vagus nerve, provided a safe and proper anchoring berth for the LINX and prevented its migration. In patients with <3 cm hiatal hernia, downward traction of the proximal stomach and the application of Positive-End-Expiratory-Pressure helps to expose the phrenoesophageal ligament and the posterior vagus nerve.

The efficacy of the LINX design has been confirmed in animals, and now in human feasibility trials. The mechanism is based on using the force of magnetic attraction to augment the resistance of the lower esophageal sphincter to gastric distention. The precise sizing of the device with the beads approximated to match the outer diameter of the resting GEJ prevents compression of the esophagus while increasing its resistance to opening by gastric distension or pressure (16-18). This concept is supported by the observation that the

<table>
<thead>
<tr>
<th>Baseline</th>
<th>1 year</th>
<th>2 year or later</th>
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<tbody>
<tr>
<td>n = 44</td>
<td>n = 39</td>
<td>n = 20</td>
</tr>
<tr>
<td>Total % time &lt; pH 4</td>
<td>11.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Upright % time &lt; pH 4</td>
<td>13.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Supine % time &lt; pH 4</td>
<td>8.3</td>
<td>2.8</td>
</tr>
<tr>
<td>No. of Episodes</td>
<td>98.8</td>
<td>27.1</td>
</tr>
<tr>
<td>No. of Episodes &gt;5 min</td>
<td>6.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Longest Episode (min)</td>
<td>36.5</td>
<td>10.7</td>
</tr>
<tr>
<td>DeMeester Score (composite of data above)</td>
<td>42.3</td>
<td>11.9</td>
</tr>
</tbody>
</table>

**TABLE 3 – Parameters of esophageal acid exposure and the composite DeMeester score (mean values) at one and two years after surgery**
device did not significantly alter the resting LES pressure in those patients who had a normal LES pressure prior to surgery. All patients in this series had the ability to belch after surgery. Dysphagia was observed during the initial postoperative period in less than half of the patients even though they were given a solid food diet on the first postoperative day. The procedure is truly reversible, in that two patients had an uneventful laparoscopic removal of the device without disrupting the anatomy of the cardia. Months later one patient went on to have a laparoscopic Nissen fundoplication. Tissue scarring at the GEJ was minimal and did not increase the difficulty of the surgical procedure.

The simple and standardized technique for insertion, and the minimal surgical dissection required to place the LINX, will likely allow for a more consistent and less variable outcome in the surgical control of reflux. Further, the short operating time and the ability to take a normal diet the day after implantation of the device make this procedure suitable for outpatient surgery.

In conclusion, the one and two-year follow-up study of the LINX sphincter augmentation device showed excellent relief of GERD symptoms and significantly reduced esophageal acid exposure without creating new side effects.

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