

Safety analysis of first 1000 patients treated with magnetic sphincter augmentation for gastroesophageal reflux disease

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SUMMARY. Antireflux surgery with a magnetic sphincter augmentation device (MSAD) restores the competency of the lower esophageal sphincter with a device rather than a tissue fundoplication. As a regulated device, safety information from the published clinical literature can be supplemented by tracking under the Safe Medical Devices Act. The aim of this study was to examine the safety profile of the MSAD in the first 1000 implanted patients. We compiled safety data from all available sources as of July 1, 2013. The analysis included intra/perioperative complications, hospital readmissions, procedure-related interventions, reoperations, and device malfunctions leading to injury or inability to complete the procedure. Over 1000 patients worldwide have been implanted with the MSAD at 82 institutions with median implant duration of 274 days. Event rates were 0.1% intra/perioperative complications, 1.3% hospital readmissions, 5.6% endoscopic dilations, and 3.4% reoperations. All reoperations were performed non-emergently for device removal, with no complications or conversion to laparotomy. The primary reason for device removal was dysphagia. No device migrations or malfunctions were reported. Erosion of the device occurred in one patient (0.1%). The safety analysis of the first 1000 patients treated with MSAD for gastroesophageal reflux disease confirms the safety of this device and the implantation technique. The overall event rates were low based on data from 82 institutions. The MSAD is a safe therapeutic option for patients with chronic, uncomplicated gastroesophageal reflux disease.

KEY WORDS: antireflux surgery, complication, gastroesophageal reflux disease, lower esophageal sphincter.

INTRODUCTION

Antireflux surgery is performed to restore lower esophageal sphincter competency, thereby treating the primary etiology of gastroesophageal reflux disease (GERD).^{1–3} Modern antireflux surgery can restore competence to the lower esophageal sphincter with one of two laparoscopic methods: either by constructing a tissue fundoplication of various degrees, or by implanting a magnetic sphincter augmentation device (MSAD) (LINX Reflux Management System, Torax Medical, Shoreview, MN, USA). The primary difference between the two options is that fundoplication uses the patient's gastric tissue to form

a plication around the lower esophageal sphincter, while the MSAD places a specifically sized mechanical device around the inferior border of the lower esophageal sphincter.^{4,5}

Fundoplication is now commonly performed laparoscopically and more recently an endoscopic approach has been introduced.⁶ The technique of forming a fundoplication can vary widely from surgeon to surgeon. Length and tightness can vary, and it can extend from a full 360° Nissen plication to a partial 270° Toupet plication, to a limited 180° Dor plication.^{7–10} Consequently, the procedure is dependent on surgical judgment and experience. This variability has limited the ability to standardize the technique of fundoplication.^{11–13} Further, since this procedure is not regulated by the Food and Drug Administration (FDA), there is no formal process to track the safety and effectiveness of the procedure, as well as the frequency of complications, which

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clouds the understanding of its actual overall safety. Consequently, the information regarding surgical fundoplication is entirely dependent on the elective publication of results. In contrast, complications related to the use of a medical device are governed by laws regarding mandatory reporting to the FDA by users and manufacturers of the devices.¹⁴

Laparoscopic implantation of an MSAD is a surgical procedure utilizing a mechanical device as an alternative to the various forms of tissue fundoplication used to treat GERD. The MSAD has been shown in controlled studies with follow-up between 3 and 5 years to provide relief of GERD symptoms, minimal long-term side effects, and the ability for the device to be removed.¹⁵⁻¹⁷ The proportion of patients reporting moderate or severe regurgitation at baseline was between 57% and 62%, and improved to 1% and 5% after the MSAD, and median total % time pH <4 was 8.0% and 10.9% at baseline, and improved to 3.2% and 3.3% at follow-up. Patients reporting discontinuation of proton pump inhibitors (PPIs) at follow-up ranged between 85% and 87%. The side effects of inability to belch or vomit were uncommon, with at least 98% of patients maintaining the ability to belch and vomit. The aim of the present study was to examine the safety profile of the MSAD in a larger number of patients than previously published and to include results from controlled clinical trials as well as clinical practice.

METHODS

In the present study, we report on the safety of the first 1000 patients implanted with the MSAD. Safety-related events were collected from three primary sources: the published clinical literature along with the device's Summary of Safety Effectiveness Data, the FDA database for device-related complications, and information provided by the manufacturer.¹⁵⁻¹⁸ Events included for the analysis were any patient-related experience that resulted in complications during or after surgery, the inability to complete the implantation of the device, a device malfunction that harmed a patient, a device-related event that required an intervention, and a hospital readmission or reoperation. The information collected for each event included the date of implant, the suspected reason for the event, and the date and type of the intervention required by the event. The timing of the events was summarized according to their occurrence as ≤ 90 days or ≥ 90 days after implantation. This differentiation allowed for the separation of events that occurred during the typical recovery of esophageal surgery (about 3 months) and those that occurred later. Additionally, events were summarized as those that were reported during the clinical trial for regulatory approval and those reported following regulatory approval.

The Medical Device Reporting regulation (MDR 21 CFR 803) requires the manufacturer of a device to track and report all significant adverse events that occur with the use of the device to the U.S. FDA. This information is filed in the Manufacturer and User Facility Device Experience (MAUDE) database.¹⁹ Medical device reports (MDRs) must be reported to the FDA within 30 days of the event. The report can be initiated by the provider, the patient, or the manufacturer. Importantly, all MDRs are made public by the FDA. The MAUDE database, a mandated reporting system of the FDA for post-market surveillance, was searched for events related to the magnetic sphincter augmentation for GERD using the device's name (LINX Reflux Management System) and the manufacturer's name (Torax Medical). The period searched in the MAUDE database extended from the date of FDA approval of the MSAD, March 22, 2012, through July 1, 2013. The authors also contacted the manufacturer for additional information about events in the MAUDE database, the estimated number of implants performed worldwide as of July 1, 2013, and a listing of any events reported by medical centers to the manufacturer not in the MAUDE database, since the manufacturer is required to have a system for tracking product complaints related to the MSAD. A summary of events included in the analysis and their source are provided in Table 1.

RESULTS

Between February 27, 2007 and July 1, 2013, 1048 patients worldwide had been implanted with the MSAD at 82 institutions in the United States and Europe. The median implant duration was 274 days. A total of 111 events occurring in 82 patients at 26 medical centers were analyzed. Of the 1048 patients, 144 were implanted as part of pre-market clinical trials, 332 had been enrolled in a post-market registry or study, and 572 were implanted outside of a post-market registry or study. Overall event rates were 0.1% intra/perioperative complications, 1.3% readmission, 5.6% esophageal dilation, 3.4% reoperation for device removal, and 0.1% device erosion (Table 2). The combined pilot and pivotal studies ($n = 144$), conducted under an investigational device exemption (IDE), had a device removal rate of 6.3% compared with 3.0% in the post-market clinical experience ($n = 904$). The combined IDE studies had a dilation rate of 13.9% compared with 4.3% in the post-market experience. The median implant duration in the combined IDE studies was 1482 days compared with 222 days for the post-market experience.

Table 1 Summary of events by source

Source of data	Number of events included in analysis	Breakout
Clinical literature	32	<ul style="list-style-type: none"> • 9 device removal • 20 esophageal dilation • 3 hospital readmissions
MAUDE database	20	<ul style="list-style-type: none"> • 19 device removal (includes US and OUS) • 1 device erosion
Manufacturer's database†	59‡	<ul style="list-style-type: none"> • 8 device removal • 1 intra/perioperative complication • 11 hospital readmission • 39 esophageal dilation

†Reports made by medical centers to the manufacturer that do not appear in MAUDE database for one or more of the following reasons: event did not meet reporting requirements for MAUDE database (e.g. esophageal dilation); event occurred prior to March 22, 2012 (FDA approval); event not yet posted at FDA website as of July 1, 2013. ‡Total of 86 events in database, 27 events were not included for the following reasons: 19 device removals reported in MAUDE database, 1 device erosion reported in MAUDE database, and 7 events did not meet inclusion criteria for analysis. FDA, Food and Drug Administration; MAUDE, Manufacturer and User Facility Device Experience; OUS, outside United States; US, United States.

Intra/perioperative complications and readmissions

No intraoperative complications were reported. One patient (0.1%) had acute respiratory arrest immediately following the implant procedure considered to be unrelated to the device. The patient was resuscitated with no additional events or clinical sequelae. The readmission rate was 1.3% for minor morbidity, such as dysphagia, pain, and nausea and vomiting. All but one readmission occurred within 90 days after the implant procedure (Table 3).

Esophageal dilations

Esophageal dilation was performed in 5.6% of patients. The majority of dilations (45/59) were per-

formed ≤ 90 days after the implant procedure. Two patients were found to have esophageal candidiasis at the time of dilation, which was reported as contributing to their difficulty in swallowing. Both patients were dilated and placed on antifungal therapy with fluconazole. No further intervention was reported.

Device removal, migration, and erosion

Device removal for any reason occurred in 3.4% of patients. Device removal rates post-regulatory approvals were 1.1% in the United States and 4.1% in Europe. The most common reason for device removal was dysphagia (2.2%) (Table 4). Median implant

Table 2 Overall summary of reported events

	Pilot IDE†	Pivotal IDE†	OUS post-approval	US post-approval	Overall
Number of patients	44	100	556	348	1048
Number of implanting centers	4	14	39	41	82
Implant duration by days – median (range)	2051 (226–2302)	1448 (21–1614)	325 (2–1308)	139 (3–448)	274 (2–2302)
Perioperative complication, % (no.)	0 (0)	0 (0)	0.2 (1)	0 (0)	0.1 (1)
Readmission, % (no.)	0 (0)	3.0 (3)	1.9 (11)	0 (0)	1.3 (14)
Esophageal dilation, % (no.)	2.3 (1)	19 (19)	4.7 (26)	3.7 (13)	5.6 (59)
Device removal, % (no.)	6.8 (3)	6.0 (6)	4.1 (23)	1.1 (4)	3.4 (36)
Device erosion, % (no.)	0 (0)	0 (0)	0.2 (1)	0 (0)	0.1 (1)
Device migration, % (no.)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Device malfunction, % (no.)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

†IDE is investigational device exemption. An IDE allows the investigational device to be used in a clinical study to collect safety and effectiveness data. OUS, outside the United States.

Table 3 Readmissions and time frame after implant procedure

Reason for readmission	Readmit ≤ 90 days after implant		Readmit > 90 days after implant	
	No. of patients	% of total implants (<i>n</i> /1048)	No. of patients	% of total implants (<i>n</i> /1048)
Dysphagia	2	0.2	0	0
Dilation and dysphagia	6	0.6	0	0
Pain	3	0.3	1	0.1
Nausea and vomiting	2	0.2	0	0
Overall	13	1.2	1	0.1

Table 4 Device removals and time frame after implant procedure

Reason for device removal	Removal ≤90 days after implant		Removal >90 days after implant	
	No. of patients	% of total implants (n/1048)	No. of patients	% of total implants (n/1048)
Dysphagia	16	1.5	7	0.7
GERD symptoms	0	0	7	0.7
Pain	1	0.1	2	0.2
Vomiting	0	0	1	0.1
MRI planned	0	0	1	0.1
Erosion	0	0	1	0.1
Overall	17	1.6	19	1.8

GERD, gastroesophageal reflux disease; MRI, magnetic resonance imaging.

duration at time of the device removal was 94 days (range 6–1302). All reoperations for device removal were non-emergent procedures. All devices were removed by a laparoscopic approach, without conversion to laparotomy or complications. Following device removal, information was available that 10 of 36 patients had a fundoplication procedure either at the time of explant or at a later time, although the number of conversions could be higher since this data were not formally tracked. For the other patients, no information was available about their management following device removal, whether it be restarting PPIs or undergoing another antireflux procedure. No device migrations were reported. One patient (0.1%) had eroded a portion of the device into the esophageal lumen. This patient presented for evaluation 20 months after implantation of the device with a complaint of dysphagia. An esophagogastroduodenoscopy (EGD) was performed and no evidence of erosion or other abnormality was observed. A second EGD, performed about 30 days later for persistent dysphagia, showed a portion of the MSAD within the lumen of the esophagus. At a third endoscopy, performed as an outpatient procedure a week later, the exposed portion of the MSAD was removed by cutting the link between the exposed magnetic beads with an Olympus Endoloop Cutter (Olympus Medical Systems, Center Valley, PA, USA). Subsequent endoscopies showed complete healing of the erosion site without sequelae. The patient elected to have the remainder of the non-eroded device laparoscopically removed about 90 days later and had a full recovery with no complications or clinical sequelae.

DISCUSSION

This analysis of the first 1000 patients treated with an MSAD for GERD assesses the safety of the device. The overall event rates for operative complications, readmissions, dilations, device removals, and device erosions were few. During the intraoperative and perioperative period, there were no events related to the MSAD that led to significant patient morbidity.

After implantation of the device in 1000 patients over a 6-year period, there were no adverse events leading to any serious long-term complications or deaths. This safety data, when coupled with the symptomatic improvement, elimination of acid suppression therapy, and reduction of esophageal acid exposure reported in controlled regulatory trials, confirm that magnetic sphincter augmentation is a highly effective and safe surgical treatment option for patients with GERD.¹⁶

Making comparisons between the MSAD and current laparoscopic fundoplication procedures is limited by the fact that the laparoscopic fundoplication has been traditionally reserved for patients with complicated GERD involving large hiatal hernia, Barrett's esophagus, strictures, and motility disorders, whereas treatment with the MSAD to date has been used primarily in patients with minimal hernias and none of the complications associated with GERD. However, both are surgical options for treating GERD, both are performed by a laparoscopic approach, and both aim to restore competency of the lower esophageal sphincter by either a device or a tissue fundoplication placed around the gastroesophageal junction. Although complications following a fundoplication are infrequent, they include such events as splenic injury, esophageal perforation, liver laceration, intra-abdominal hemorrhage, pneumothorax, subphrenic abscess, small bowel perforation, and hematoma in the fundoplication.^{20–22} The initial experience with implantation of an MSAD had none of these complications. The likely reason is that implantation of MSAD does not require extensive dissection of the gastric fundus or esophageal hiatus. The minimal dissection required for the implantation of the MSAD leaves the phrenoesophageal ligament undisturbed and intact, and likely reduces the risk of complications or the migration of the device.

A recently introduced alternative to laparoscopic fundoplication is the transoral incisionless fundoplication (TIF) (EsophyX device, EndoGastric Solutions).²³ The TIF repair is an endoscopic partial fundoplication option for GERD, using transmural

tissue fasteners, that should minimize postoperative side effects. The major complication reported with this approach is esophageal perforation, which can extend hospitalization for several weeks. Other reported complications following TIF include mediastinal abscess formation, esophagopulmonary fistula, septic shock, permanent numbness of the tongue, and hemorrhage requiring transfusion.^{24–26} In addition, conversion rates of TIF to laparoscopic fundoplication have been reported between 11.5% and 52.6%.^{25,27–29} The initial experience with implantation of an MSAD had none of these complications. Again, the minimal dissection required for the implantation of MSAD avoids the complications associated with inserting fasteners through the gastric and esophageal walls as is done with TIF.

A common side effect after either implantation of an MSAD or fundoplication is temporary or persistent dysphagia. When the MSAD experience is compared with another large experience of at least 1000 patients who underwent fundoplication, the 5.6% dilation rate for dysphagia after MSAD was comparable to the 6.4% after fundoplication.³⁰ This is notable given that patients go directly to a solid food diet following implantation of an MSAD compared with a several-week soft food diet after fundoplication. The temporary dysphagia for both procedures may be due to tissue edema that develops at the site of dissection and eventually resolves over the ensuing weeks. Additionally, in the case of fundoplication, crural approximation may contribute to symptoms of dysphagia as well.

The criteria for when to perform dilations for dysphagia after the implantation of an MSAD are not yet standardized. There has been a tendency for physicians to dilate early in the postoperative course. With more experience, the management of dysphagia after implantation of an MSAD may evolve from early intervention to a ‘wait and see’ approach, and with this evolution the overall incidence of dilations may decrease. This trend may already be developing since dilation rates in the United States post-FDA approval are 3.7% in contrast to the dilation rate of 19% in the pivotal trial.¹⁶ A similar trend was observed in the management of post-fundoplication dysphagia. In a series of 400 consecutive fundoplications, the use of endoscopic esophageal dilation for dysphagia decreased over time as the surgeon gained experience. In the early fundoplication experience, 16–18% of patients were dilated during the first 10 months postoperatively compared with 4–10% who were dilated during the first 7 months at the midpoint of their experience.³¹ Additionally, dilation rates after fundoplication were lower for more experienced surgeons, with trainees reporting a 9% rate compared with 5% for experienced surgeons.³² As more experience is gained in managing patients implanted with the MSAD, the

rate of dilations is likely to decrease similar to the pattern after fundoplication.

With any antireflux surgical procedure, surgical revisions may be needed. The reported revision rate after laparoscopic fundoplication ranges between 2% and 17%, and after an endoscopic TIF between 11.5% and 52.6%.^{25,27–29,33–35} Revision of laparoscopic fundoplication is associated with a higher rate of complications and morbidity than the original procedure, ranging from 0% to 44%, with an overall postoperative complication rate of 14%.^{36,37} Due to the complexity of redo operations, safe and positive clinical outcomes are highly dependent upon the surgeon’s skill in the reestablishment of normal hiatal anatomy, the management of a short esophagus, and the proper placement of the fundoplication.³⁸ The reoperation rate for any reason after implantation of an MSAD was 3.4%, and all were performed by a laparoscopic approach without the need to convert to a laparotomy. No intraoperative or postoperative complications occurred in conjunction with removal of the device. Further, with the MSAD procedure, the hiatal and gastric anatomy remains undisturbed, allowing a subsequent fundoplication to be performed.^{16,17} In the pivotal IDE study, three of six device removals were followed by fundoplication, and in another series of 100 patients, three of three device removals were followed by fundoplication.^{16,17}

In this analysis, there was one reported event of erosion where a portion of the MSAD was visible in the esophageal lumen. The risk of erosion is a known concern when a foreign body is placed around the esophageal body with its constant dynamic movement and the perpetual motion of the adjacent diaphragm. Because the MSAD is a small device and distensible, the risk of erosion is assumed to be very low, as has been observed in this analysis. We believe it is important to deploy a minimal dissection technique to minimize this risk. Based on a very limited experience, it appears that should MSAD-associated erosion occur, it can be managed conservatively with an endoscopic approach with minimal complications or clinical sequelae.

The readmission rate after the implantation of an MSAD was 1.3% and is lower than that reported for a fundoplication. In a review of 10 studies on fundoplication, the readmission rate was 5%.^{39,40} The most frequently cited reasons for readmission after fundoplication were similar to those after MSAD implantation, namely dysphagia, pain, nausea, and vomiting. The low readmission rate after implantation of an MSAD emphasizes that the procedure is well tolerated and less likely to induce the postoperative complaints associated with a fundoplication.

Differences between MSAD and fundoplication need to be interpreted with care since the typical patients treated with MSAD generally do not have a large hiatal hernia or other comorbidities, such as

Barrett's esophagus, strictures, or motility disorders to the same extent as patients who typically undergo fundoplication. An additional limitation of this safety analysis is its reliance on health professionals to consistently report events occurring outside of a clinical study to the manufacturer and/or FDA. Even though there is a potential for underreporting of complications in the post-approval period when patients are not carefully followed under a protocol, the process and procedures in place for a medical device still provide a formal mechanism for reporting adverse events to the FDA that is not for other procedures. This report shows the MSAD, when used in a wide range of clinical settings for uncomplicated GERD, provides a safe alternative to fundoplication, with a low number of complications or reports of unanticipated adverse events. It appears that the overall safety profile in early clinical practice is as good or superior to what was observed during the clinical trials. This is important considering that the safety of new technologies often diminishes when outside the controls of a clinical study. It should be noted that the typical surgeon implanting the MSAD had already demonstrated proficiency in performing laparoscopic fundoplication and was comfortable working at the gastroesophageal junction. The learning curve appears to be similar for both procedures based on the authors' experience.

In conclusion, the MSAD has a low risk profile, and the overall device removal rates are relatively low. The hiatal and gastric anatomy is left undisturbed, thereby keeping the option for fundoplication if the device is removed. This safety analysis of the first 1000 patients underscores that the MSAD is a safe option for patients with uncomplicated GERD who are considering antireflux surgery.

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