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Update in Procedural Therapy for GERD – Magnetic Sphincter Augmentation, Endoscopic Transoral Incisionless Fundoplication vs Laparoscopic Nissen Fundoplication

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Abstract Gastroesophageal reflux disease (GERD) is a common and progressive condition manifested by heartburn or regurgitation. Though Nissen fundoplication has been and remains the gold standard for procedural therapy for GERD, two newer interventions have gained popularity: magnetic sphincter augmentation (MSA), which entails the placement of a self expanding magnetic ring around the gastroesophageal (GE) junction, and transoral incisionless fundoplication (TIF), an endoscopic approach that creates a neogastroesophageal valve near the fundus. Collective data gathered from four studies published within the past year suggest that the three modalities share comparable effectiveness in pH monitoring and patient satisfaction, TIF may have a lower proton pump inhibitor cessation rate, and Nissen fundoplication required longer recovery time and had a more serious adverse effects profile. Large, prospective, randomized controlled studies are needed to reliably compare the three procedures.

Keywords Gastroesophageal reflux · Proton pump inhibitor · Nissen fundoplication · Magnetic sphincter augmentation · Transoral incisionless fundoplication

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Introduction

Gastroesophageal reflux remains a major disease burden despite the successful advent of medical therapy. First-line treatment for gastroesophageal reflux disease (GERD) is acid-suppression typically employing proton pump inhibitors (PPIs); however, a significant fraction (up to 40 %) of GERD sufferers remain at least partially symptomatic despite use of these agents [1–3]. In addition, PPI therapy can be associated with side effects, and medical therapy does not address the underlying pathophysiological defects leading to GERD. Patients either failing or unwilling to take long-term anti-reflux medications have typically turned to Nissen fundoplication surgery as the standard, established non-medical treatment option. Nissen surgery is widely considered to be highly effective; however, the procedure has had limited acceptance due to significant adverse events such as bloating, and inability to belch or vomit [4, 5]. Consequently, over the past 10–15 years, many surgical and endoscopic alternatives to Nissen surgery have been introduced. This paper will examine the most recent literature involving two of these alternatives; a laparoscopic surgical approach employing a magnetic implant to augment the lower esophageal sphincter (LES) using the LINX system (Torax Medical), and an endoscopic fundoplication approach, i.e. transoral incisionless fundoplication (TIF; EndoGastric Solutions), as compared to traditional Nissen surgery.

Description of Procedures

Nissen Fundoplication

The original Nissen procedure (Fig. 1) was performed by Dr. Rudolph Nissen in 1955 [6]. The procedure involved passing the gastric fundus behind the esophagus to encircle the distal

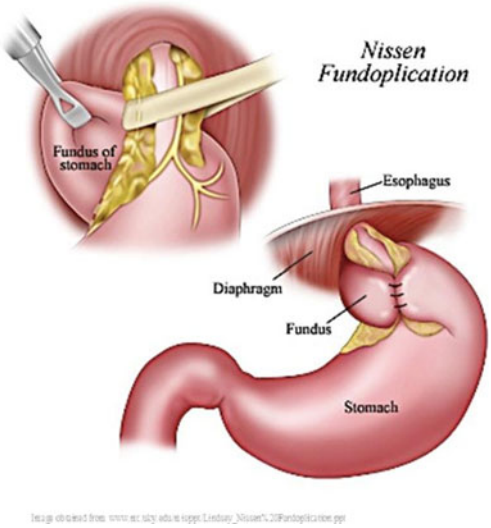

Fig. 1 Nissen Fundoplication

end of the esophagus. The procedure was at first performed via open approach, either trans-abdominal or trans-thoracic, with laparoscopic fundoplication (LNP) introduced into clinical practice in 1991 [7]. LNP remains the most frequently performed operation for GERD [8]. The laparoscopic approach has been associated with comparable safety profile, better patient satisfaction, as well as shorter hospital stays when compared to the open procedure [9]. Despite its advantages, the laparoscopic approach still shares a similar side effect profile as the open approach including post-operative dysphagia and gas bloat syndrome [10, 11]. For this reason, there have been recent efforts in the surgical community to pursue different variations of the original Nissen fundoplication. The majority of these variations pertain to partial fundoplication, including posterior 270-degree, anterior 90-degree, and anterior 180-degree approaches [12].

Transoral Incisionless Fundoplication (TIF)

Endoscopic suturing and plicating approaches for treating GERD were first introduced in the year 2000. The first of its kind, EndoCinch, involved an endoscopic sewing device, and has fallen out of favor due to its lack of long-term efficacy [13]. The TIF procedure is a relatively new, endoscopic anti-reflux procedure that recreates a sphincter using tissue from the fundus (Fig. 2). During upper endoscopy, a large endoscope with a channel for a video scope is inserted into the mouth and turned to face the gastroesophageal (GE) junction. Under direct visualization of the endoscopist, a tissue grasper is passed through the retroflexed endoscope in the region of the GE junction. A portion of the fundus tissue is grasped and pulled distally, creating a two-layer overlap of the stomach. A needle guide wire is passed out of the endoscope through the two layers of tissue, then a double-sided tag is inserted over

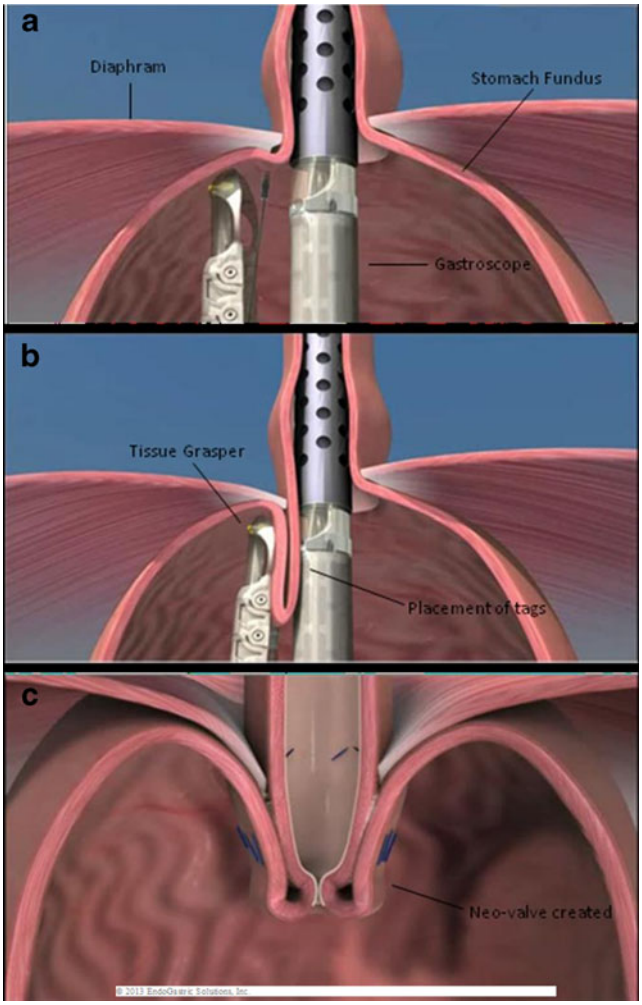

Fig. 2 Trans-oral incisionless Fundoplication

the guide wire, and released on the fundic side of the duo-layer that was just created to stabilize the shape of the plication. The endoscope is then rotated and the above process is repeated until a near-circumferential neo-gastroesophageal valve of approximately 260 degrees is formed [14].

Magnetic Sphincter Augmentation (MSA)

The magnetic sphincter device is a self-expansible bracelet of magnetic beads hermetically sealed in titanium cases and connected by titanium wires, that augment the native LES (Fig. 3). The beads each have a hollow center that allows them to freely slide away from one another along the wire during a bolus swallow. The bracelet is surgically implanted around the exterior surface of the GE junction. When the patient initiates a swallow, the peristaltic bolus exerts pressure on the bracelet and forces on the magnetic beads to separate from one another, allowing the swallowed content to pass into the stomach. The end of the peristaltic motion initiates re-attraction of the bracelet magnets restoring augmentation of the LES to prevent

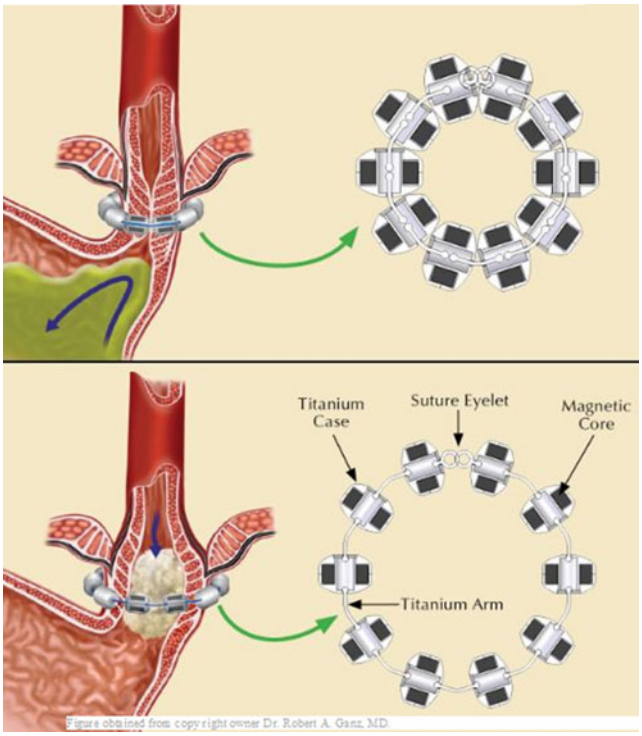

Fig. 3 Magnetic sphincter augmentation

reflux. Inside each bead is a collection of small disk-shaped magnets with set sizes and masses designed to achieve the desired degree of magnetic force. The most unique aspect of magnetic sphincter augmentation when compared to other procedural interventions for GERD is its intrinsic and perpetual capacity to self-adjust and react to external forces with exponentially varying degrees of resistance. The degree of magnetic force between the beads when the bracelet is at rest is strong enough to augment the sphincter and prevent pathological reflux, while at the same time weak enough to allow belching and not cause dysphagia in most cases. This surgery is routinely done laparoscopically without need for antibiotics and with same day discharge and immediate resumption of a normal diet. The surgery itself requires minimal dissection and maintains the integrity of the physiology and anatomy of the GE junction [15•].

Comparative Analysis

Despite the fact that there have been numerous recent clinical studies regarding each of the above procedural entities, there have been no randomized controlled trials with head-to-head comparisons between MSA, TIF, and/or fundoplication. Furthermore, there is great variation in the design of these studies, including sample size, length of follow-ups, patient selection, and clinical endpoints, making it challenging to construct cross-procedural comparisons. For example, the TIF procedure has been limited to patients without a physiologically significant hiatal hernia, MSA has been limited to patients with a small hiatal hernia, and there has been no hernia size restriction for LNP studies. Nissen fundoplication surgery, given its long history, has yielded the most abundant data as well as longest follow up, routinely greater than 10 years [16, 17, 18•], with more recent studies on variations of the procedure lasting up to 5 years [18•]. MSA has had fewer studies, but follow-ups have been as long as up to 5–6 years [15•, 19•]. The TIF studies have had shorter follow-ups on average, with one long-term study lasting up to 3 years [20•].

The aim of this manuscript is to interpret important complete publications from each of the three therapeutic fields within the past 12 months and to attempt to make comparisons of both subjective and objective data following said procedures. Utilizing PubMed, the full names of LNP, TIF, and MSA were entered into the search field and studies were sorted by date of publication. Studies with comparable cohorts and study design were included in the review. Published abstracts were not included. For MSA, 2 papers were identified: Ganz, 100 patients, length of study 3 years (of a planned 5-year study) [15•], and Bonavina, 100 patients, length of study 6 years [19•]; for LNP, 1 paper was identified: Kellokumpu, 249 patients, 10-year study [18•]; for TIF, 1 paper was identified: Muls, 66 patients, 3-year study [20•]. Several recently published review articles were used for supplemental data and perspective.

pH Monitoring

Esophageal pH monitoring is the most objective way to document pathological GERD, and is commonly used to assess success of therapy. Ganz reported pre- and post-MSA fraction % time pH<4 at 8 and 3.2 %, respectively ($p<0.001$) [15•]; Bonavina reported similar findings, with pre- and post-MSA pH at 10.9 and 3.3 %, respectively ($p<0.001$) [19•]. Only 11/54 patients in the Muls study underwent pH testing, with pre- and post-TIF acid reflux times of pH<4 at 9 and 3 %, respectively [20•]. In the LNP study, there was no reported consistent pH monitoring either before or after surgery. However, it was reported that, in the 32 patients that underwent pH measuring at the time of 10-year follow-up, the 6 patients that were noted to have displaced fundoplication had pH<4 on average 25.1 % of the time, whereas the 26 patients who had intact fundoplication had pH<4 on average only 0.6 % of the time [18•].

PPI Cessation

The need for continued use of proton-pump inhibitors (PPI) post-procedure is another objective way to measure outcome. All the cited studies included only GERD patients who had failed PPI therapy. The two MSA groups reported a similar rate of PPI cessation, with the Ganz cohort demonstrating

complete PPI cessation in 87 % at 3-year follow-up ($p<0.001$) [15•], and Bonivana 85 % at 6-year follow-up [19•]. For the TIF procedure publication, 86 % of patients were able to completely come off PPI therapy at 1-year follow-up, and 74 % at 3-year follow-up ($p<0.06$) [20•]. In the LNP group, it was reported that 72.9 % still showed some degree of PPI reliance at 10.2 years of follow-up, and 7.9 % of those who were not using PPI reported daily to weekly symptoms [18•]. A review article published by Broeders summarizing 2 trials on LNP reported complete PPI cessation in 92.6 % (112/121) at 1 year, 90 % at 5 years, and 86 % beyond 5 years following procedure [21].

Symptom Improvement

Symptom improvement after therapy is another important indicator for assessing success of treatment; however, symptom control scores are subjective and prone to bias in uncontrolled trials. The GERD Health-Related Quality of Life (GERD-HRQL) is a validated and standardized assessment tool comprised of 10 questions with a numerical grading scale and one qualitative question [22], and was used in the MSA and TIF publications. Bonavina reported GERD-HRQL score improvement from 24 to 2 after procedure off PPI therapy ($p<0.001$); Ganz reported similar findings of 27 to 4 ($p<0.005$) [15•, 19•]. Muls reported improvement from 25 to 4 at 3 years off PPI ($p<0.0001$) [20•]. A review article published by Wendling reported that, in 10 previously published TIF studies, the GERD-HRQL score improved on average from 21.9 to 5.9, with a mean follow up of 9.8 months [23]. At the time of web-search for this article, there were no recent publications of LNP that utilized the GERD-HRQL scale as a tool to assess improvement.

Satisfaction

With regard to overall satisfaction of management of GERD, patients were polled using varying forms of a questionnaire with selections of satisfied, neutral, or unsatisfied. For magnetic sphincter augmentation, Bonavina reported an improvement from 5 % satisfaction before surgery to 87 % post-MSA implant; the Ganz group reported similar findings with improvement from 13 to 94 % [15•, 19•]. The Muls TIF study showed satisfaction improvement from 6 to 74 % [20•]. Wendling's review of 12 TIF studies reported a range of 45–87 % satisfaction post-endoscopy, with an adjusted average of 72 % [23]. In the review article on LNP reported by Broeders, 88 and 98 % of patients were satisfied with the procedure at 5 years and beyond 5 years, respectively [21]. For LNP, Kellokumpu reported that 82.8 % of patients were satisfied with disease management at time of follow-up, with 84.9 % of patients willing to undergo surgery again, whereas 15.1 % of patients would have chosen medical therapy instead [18•].

Complications and Procedure Failure

For the MSA procedure, Bonivana reported no complications, and three patients required device removal at 378, 771, and 406 days post-implantation, all due to persisting symptoms of odynophagia, GERD, or dysphagia. All 3 patients subsequently went on to have either a Dor fundoplication, Toupet fundoplication, or a Lortat-Jacob anti-reflux procedure post-explantation, with immediate relief of symptoms. Ganz reported no complications, and 3 patients underwent device removal at 21, 31, and 93 days post-implantation for dysphagia, with subsequent relief of symptoms; 3 patients needed device removal at 489, 357 and 1062 days for persistent GERD, nausea and vomiting, or chest pain; and 3 of the 6 patients underwent successful Nissen fundoplication [15•, 19•]. In the Muls TIF study, 12 patients underwent a revision procedure, with 2 needing LNP and 10 needing repeat TIF procedures [20•]. In the Kellokumpu LNP study, 3 cases of intra-operative esophageal or fundic perforation were reported; at the time of the 10.2 years follow-up, 4.3 % of patients had undergone reoperation for reflux recurrence caused by defective fundoplication [18•].

Hospital Stay

On average, patients undergoing LNP required 2–3 days of hospital stay, whereas those undergoing MSA or TIF required 0.75–1 day of hospital stay. All 3 procedures took approximately 1 hour to complete.

Conclusion

Based on data from this past year, LNP remains the most utilized non-medical intervention for GERD, with no limits on hiatal hernia size or severity of GERD. The most recent LNP study had the largest sample size, and longest follow-up compared to the other 2 procedures but had limited pH data. Despite its relative popularity, this procedure is accompanied with a notable, well-recognized side effect profile, longer procedure time and hospital stay, and significant failure rate, i.e. continued reliance on daily PPI and need for reoperation. Compared to LNP, the studies on magnetic sphincter augmentation were limited to GERD cohorts with small hiatal hernias, although these studies included relatively large sample sizes, robust end-points with complete pH data, and relatively long study follow-up. Given the solid published MSA data, the removable nature of the magnetic implant, and the nominal anatomical changes that are required by this procedure, magnetic sphincter augmentation appears to be an attractive alternative to LNP, for selected cohorts of GERD patients failing PPIs. The TIF procedure shows promise as its endoscopic nature should ideally yield a less significant side effect profile; however, the endoscopic wrap created is partial, and the

limited data pertaining to this approach, particularly the small number of long-term follow-up studies and the incomplete pH data, limit its current clinical application. The TIF procedure is additionally limited to patients without physiologically significant hiatal hernias. Large, randomized, head-to-head, prospective studies, with comparable GERD cohorts and long-term follow-up, are needed to reliably compare these 3 procedures.

Compliance with Ethics Guidelines

Conflict of Interest Robert Ganz has no conflicts of interest. Michael Min has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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