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Endoscopic therapies for gastroesophageal reflux disease

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ABSTRACT

Gastroesophageal reflux disease (GERD) accounts for a substantial degree of medical resource utilization and is a common indication for outpatient physician visits. The primary therapy for GERD has been proton pump inhibitors (PPIs). Equally effective and reasonably safe for GERD is surgical therapy, specifically, laparoscopic Nissen fundoplication. Medical therapy is used initially, with surgery reserved for patients with refractory symptoms despite optimal medical management, to avoid the added risks of abdominal surgery. As such, there has been considerable investigation into minimally invasive, endoscopic therapies for patients who respond to PPI, but would prefer to avoid long-term medication use. Here, we discuss the anatomical and physiological barriers that must be overcome by such devices. We further review the data on currently available endoscopic devices. Despite considerable interest and resources in developing an effective endoscopic therapy for GERD, none of the currently available technologies have demonstrated an ability to overcome the pathophysiological hurdles present in most patients with GERD. Furthermore, well-designed trials have not demonstrated adequate clinical efficacy for these endoscopic devices. As such, despite a growing need for an intermediate therapy between PPI and fundoplication, at present there is not adequate evidence to recommend endoscopic therapy for patients with GERD.

1. Introduction

Gastroesophageal reflux disease (GERD) is a common condition with substantial medical resource utilization [1]. The mainstay of therapy is pharmacologic with antacids and histamine receptor antagonists used for occasional symptoms. In patients with frequent symptoms or with complications of acid reflux (esophagitis and stricture or Barrett esophagus), the mainstay of therapy is proton pump inhibitors (PPIs). PPIs have demonstrated significant efficacy for the treatment of GERD and multiple trials have shown that PPI therapy is more effective than placebo and histamine receptor antagonist for healing erosive esophagitis [2,3]. In addition, PPI therapy has also demonstrated efficacy in high-quality studies for symptom control in patients with nonerosive reflux disease [4].

Despite the benefits and demonstrated efficacy of PPI for managing symptoms and reflux-related esophageal injury, there exists a subpopulation of patients for whom PPI may not be the ideal long-term therapy. This includes patients who have reflux-related symptoms despite adequate PPI dosing, nonhealing erosive esophagitis, persistent heartburn, and extraesophageal symptoms (ie, cough). It also includes patients who are intolerant or unwilling to accept the side effect profile of PPI, specifically those concerned about bone health. In such patients, the primary nonpharmacologic therapy has been Nissen fundoplication. Over the past 15 years, this technique has been modified to a minimally invasive laparoscopic approach, which is associated with decreased recovery time and acceptable safety profile in the hands of an experienced foregut surgeon [5].

There is a large gap in regard to safety, up-front cost, and patient acceptance between medical therapy and laparoscopic Nissen fundoplication (LNF.) This gap has resulted in the development of several endoscopic, noninvasive therapies. The early enthusiasm for several of these devices has been tempered by the lackluster efficacy in well-controlled trials as well as safety concerns with some of the devices. This has led to waning interest in endoscopic devices as an alternative to LNF. At this point, there are 2 endoscopic devices that are available for commercial use, Stretta (Mederi therapeutics, Greenwich, CT) and Esophyx (EndoGastric solutions, Redwood City, CA). In this review, we discuss the physiological barriers that must be overcome by a successful antireflux therapy, and review the current literature for the available endoscopic devices.

2. Pathophysiology of GERD

GERD is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms or complications

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or both [6]. It requires the retrograde flow of acidic gastric contents to come in contact with the esophageal epithelium. These events can result in symptoms of heartburn. Prolonged episodes can lead to esophagitis, Barrett esophagus, and esophageal stricture. The primary mechanism to prevent reflux of gastric contents is a mechanical barrier at the esophagogastric junction (EGJ). This barrier is created by the lower esophageal sphincter (LES) and the crural diaphragm. Once a reflux event occurs, rapid emptying of the esophagus results in clearance of the refluxate, thus minimizing the exposure time of the esophagus to the caustic gastric contents.

The primary mechanism for pathologic reflux is an incompetent antireflux barrier. This occurs as a result of diminished tone at the LES or possibly related to mechanical alterations that reduce the pressure threshold required to open the EGJ. In the absence of a hiatal hernia, the primary aberration is an incompetent LES. Hiatal hernia provides a unique physiological challenge, whereby separation of the crural diaphragm from the LES ultimately renders the LES ineffective as an antireflux valve. In addition, the stomach is displaced proximally, thus allowing gastric contents unimpeded access to the esophageal epithelium. This is especially problematic when supine. It is of considerable significance to note that one of the dominant contributors to EGJ pressure is the crural diaphragm, and hence, therapies that do not adequately address a substantive crural defect are likely to be less successful than surgical repair [7]. An effective endoscopic therapy must be able to overcome the unique physiological challenges that are inherent in patients with severe reflux.

3. Devices no longer available

There have been several devices that have been studied for reflux that are no longer commercially available. These include EndoCinch (Bard Medical), Endoscopic Plicator system (NDO Surgical), and Enteryx (Boston Scientific). We discuss them briefly to provide historical context for the approach to endoscopic therapy in GERD. Enteryx was a polymeric bulking agent that was injected into the LES using a standard sclerotherapy needle. The goal was to augment the tone of the LES. Early studies revealed improvement in symptoms and decrease in PPI use; however, objective measures of percentage acid exposure time (%AET) showed modest or no change [8-10]. Enteryx was voluntarily taken off the market in 2005 as a result of multiple reported serious adverse events related to mediastinal infection or abscess secondary to the polymer material.

EndoCinch was manufactured by BARD medical, and was one of the first devices to attempt to mimic the effects of a surgical fundoplication by creating an endoscopic plication. The plication was not full thickness. Two randomized, sham-controlled trials revealed improvement in symptoms 3 months postprocedure, but no substantive improvement in %AET compared with sham. In addition, the symptom improvement was not sustained at 12 months postprocedure [11,12]. The EndoCinch is no longer used for reflux, but has been studied for gastric pouch reduction in patients who have gained weight after gastric bypass [13]. The Endoscopic Plicator System also attempted to mimic surgical fundoplication, but unlike EndoCinch, was able to create a full-thickness transmural gastric plication. One randomized, sham-controlled trial revealed significant improvement in objective parameters, with modest improvement in objective parameters at 3 months postprocedure [14]. Longer follow-up revealed sustained improvement in symptoms; however, %AET was, again, only modestly improved.

4. Currently available devices

At present, there are only 2 endoscopic devices for reflux that are available in the United States. The first is Stretta. The device consists of a balloon that is encased by a basket that contains metallic electrodes. The electrodes are connected to a radiofrequency energy delivery device. The balloon is inflated in the distal esophagus at the level of the EGJ and the electrodes burrow in the esophageal mucosa. Radiofrequency energy is delivered with the goal of resulting in submucosal fibrosis. Stretta was 1 of the first endoscopic antireflux devices available in the United States. There are considerable high-quality data evaluating its efficacy. The second available endoscopic device is Esophyx. The Esophyx device is the only endoscopic device that can create circumferential, serosa-to-serosa gastric plications, and most closely mirrors the effect of a surgical fundoplication. Though there are no randomized controlled trials (RCTs) of Esophyx, prospective comparative studies are ongoing.

4.1. Stretta

Early exploratory data using Stretta revealed relative safety and improvement in patient's symptoms and overall quality of life 3 months postprocedure. This led the framework for a large prospective open label study of 118 patients who underwent Stretta procedure, with 12-month follow-up. Subjective parameters, such as GERD-Health Related Quality of Life (HRQL), short form-36, and patient satisfaction, were collected, along with objective measures, such as esophageal manometry and ambulatory pH testing. The authors report significant improvement in all subjective measures up to 12 months postprocedure. They also report a dramatic decrease in %AET from 10.2-6.4 [15]. Surprisingly, LES pressure also decreased, and as such, the physiology of the improved %AET is unclear. This study led the way for higher quality RCT to more carefully study the efficacy of Stretta. In total, 3 large sham-controlled RCTs were performed to evaluate Stretta.

The first study was multicenter and sham controlled. Symptom improvement was the primary endpoint. Secondary end points included PPI use, LES pressure, and change in %AET. At 6 months postprocedure, the treatment arm had significant improvement in heartburn score, HRQL, and short form-36 compared with sham [16]. Unlike the open label studies, there were no improvements in any of the objective measures or in medication use.

The second RCT included 3 arms: sham, single-dose, and double-dose Stretta. Again, objective and subjective measures were collected and evaluated. Unlike the first RCT, there was no significant improvement in GERD-HRQL in the treatment arm compared with the sham arm. There was modest improvement in %AET in both the sham arm and treatment arm. No change in LES pressure was noted [17]. The last RCT was perhaps the most rigorous with both investigator and patient blinded to the treatment. It was a crossover study with all patients acting as an internal control, and all patients receiving therapy by the end of the study. At 3 months, there was significant improvement in symptoms in the treatment group compared with sham. In patients who received sham initially, there was significant improvement in symptoms after receiving Stretta. Similar to the other studies, there was no improvement in %AET, LES pressure, or PPI usage [18].

4.1.1. Summary

Despite promising open label studies, the efficacy of Stretta for the management of reflux has not been demonstrated in high-quality studies. It is interesting to note that subjective improvement in symptoms was consistently demonstrated, even in sham-controlled studies. This has led to the hypothesis that radiofrequency energy delivered to the esophageal mucosa may decrease visceral sensitivity. Objective parameters such as %AET, LES pressure, and PPI use were not improved by Stretta. In addition, there have been reports of