REVIEW

Endoscopic Antireflux Procedures: A Good Wrap?

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Background & Aims: **Gastroesophageal reflux disease (GERD) is prevalent worldwide. Until recently patients and physicians have had a choice between long-term medical therapy, usually in the form of proton pump inhibitors (PPIs), or surgical fundoplication. During the past several years, endoscopic antireflux therapies have been approved for GERD patients to potentially obviate the risks of surgery and avoid long-term medication use. The objective of this review was to critically evaluate existing literature on endoscopic antireflux therapies with regards to efficacy and safety.** ***Methods:*** **A review of human studies by using Pub Med was performed.** ***Results:*** **Injectable LES implants, endoscopically placed gastric plications, and radio frequency energy application to the LES comprise the 3 modes of antireflux therapies. These techniques received approval by the Food and Drug Administration on the basis of symptomatic evidence supplied by numerous uncontrolled trials. As a group, these techniques have demonstrated efficacy less than medical and surgical options, and yet they carry a rare but significant risk of serious complications and even death.** ***Conclusions:*** **The field is still evolving at this stage, and there is a need for more randomized sham and placebo-controlled trials to better define the subjective and objective outcomes of these endoscopic procedures. At this time endoscopic antireflux procedures should be used with caution after discussing risks and benefits with the patient.**

Gastroesophageal reflux disease (GERD) is both costly and widely prevalent. There are almost 4.6 million GERD-related clinic visits every year in the US alone.[1] The estimated annual cost has been estimated to be $9.3 billion dollars in 2000.[2] Greater than 60% of this burden is related to the cost of antisecretory medications.[3] In addition to quality of life issues, the numerous complications of chronic GERD such as esophagitis, esophageal stricture, intestinal metaplasia, and esophageal adenocarcinoma necessitate adequate treatment of this entity.

The range of therapeutic options has rapidly evolved to include numerous pharmacologic possibilities, open and laparoscopic surgical techniques, and the more recently heralded endoscopic antireflux procedures. Medical therapy not uncommonly results in failure to completely control symptoms, the long-term costs of proton pump inhibitors (PPIs) is significant, and patients might prefer to avoid daily pill taking.

Until recently the nonpharmacologic approach to GERD has been surgical. Laparoscopic fundoplication has been suggested as the gold standard for patients with more severe GERD.[4] However, despite its potential advantages, many patients are not willing to accept the inherent risks of surgery, and some are simply not surgical candidates as a result of comorbid conditions. There has therefore been a great deal of interest in endoscopic modalities that would obviate surgical risk. The initial enthusiasm for these techniques is typical of any novel and innovative option, but the evidence of their effectiveness is not impressive and is largely based on uncontrolled clinical trials.

There are currently 3 main endoscopic modalities available to GERD patients. The first method involves the injection of an inert material into the LES. The second broad category uses various methods of endoscopic suturing to create an effect similar to that of surgical fundoplication. The third method is the application of thermal energy near the gastroesophageal junction. Each technique was relatively rapidly approved by the Food and Drug Administration (FDA) for use in human beings on the basis of the previously mentioned uncontrolled studies showing them to be "substantially equivalent" to existing therapies.

The objective of this review was to critically evaluate the existing evidence on endoscopic antireflux therapies with regards to efficacy, safety, and technical feasibility. We performed a review of the English language litera-

Abbreviations used in this paper: FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; RFE, radio frequency energy; tLESR, transient lower esophageal sphincter relaxation.

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ture by using PubMed, limiting our evaluation to human studies. Our goal was to determine whether any of these new techniques should be adopted into routine clinical practice. We also aimed to highlight specific areas in need of more comprehensive investigation.

Lower Esophageal Sphincter Implants

LES implant experimentation on dogs' LE sphincters was initially performed in 1984.[5] This led to a pilot human study by the same group in 1988 in which bovine collagen was injected into the LES.[6] Several studies of small series with suboptimal injectables were subsequently published.[7,8]

As the search for a better implant continued, it was noted that ethylene-vinyl alcohol co-polymer (Enteryx; Boston Scientific, Natick, MA) had been successfully used in embolization of arteriovenous malformations. The substance has a low viscosity, making it much easier to inject, and on contact with tissue precipitates into a spongy mass. In 2002, a pilot study to evaluate the safety of Enteryx for GERD was published.[9] During the short-term follow-up of 6 months, there were no significant complications apart from self-limited retrosternal chest discomfort up to 3 days after procedure and 1 case of transient dysphagia. The study was not powered to evaluate for efficacy. The follow-up prospective multicenter trial involving 85 PPI-responsive GERD patients was uncontrolled but designed to evaluate efficacy[10]; 76.5% of patients were considered responders with a reduction in PPI use by at least 50%. Heartburn and regurgitation symptoms were significantly improved at 12 months. Thirty-eight percent of patients achieved normalization of esophageal pH at 12 months when normalization was defined as pH <4 less than 5% of the time. There was no significant change observed in the LES pressures. The procedure required fluoroscopic and endoscopic guidance during implantation. If Enteryx was not precisely injected into the muscular layer, investigators noted a significant loss of the implanted material during short-term follow-up. Dysphagia was reported in 20% of patients and could last for up to 12 weeks. To date, many more patients have undergone the procedure outside the context of a clinical trial. Two patients have died as a result of the Enteryx procedure. The first patient developed an esophageal abscess and subsequent progressive renal failure requiring hemodialysis.[11] She died suddenly during her fourth session of dialysis, and no autopsy was performed. The second patient died after developing an esophageal-aorta fistula that resulted in massive, uncontrollable gastrointestinal hemorrhage. The autopsy revealed 2 esophageal ulcerations 1 cm above the gastroesophageal junction, extensive inflammation, a fistula between the esophagus and aorta, and Enteryx material in the superficial wall of the aorta.[12]

The most recent endoscopic antireflux study evaluated another evolution in LES implantation, the Gatekeeper Reflux Repair System.[13] The method consists of the insertion of expandable polyacrylonitrile-based hydrogel prostheses by using an overtube and mucosal suction technique without the use of fluoroscopy. The study showed a reduction in symptoms at 6 months, improvement in esophageal acid exposure, increase in the LES pressure, and a statistically significant increased quality of life by physical composite score. The use of PPI medication was poorly followed. Some centers used general anesthesia, and the procedure had to be repeated in almost 15% of patients. One patient experienced a pharyngeal perforation during overtube insertion, which precipitated a 1-week hospital stay without surgical intervention. Another patient reported postprandial nausea for 1 week and had all 3 of her prostheses successfully removed without complication, leading to relief of symptoms. The most common adverse event reported was erosion over the prosthesis site, which increased in incidence during the 6-month follow-up.

Endoscopic Plications

Interest in endoscopic suturing to create plications was a by-product of the success of both open and laparoscopic fundoplication. Swain and Park[14] were the first to develop these techniques as a therapeutic option in human beings. The EndoCinch system involves a suturing capsule attached to the end of a conventional endoscope, knot pusher, and suture cutter developed by Bard Interventional Products, Covington, GA. In 2001, Park et al[15] published an abstract using EndoCinch in a series of 142 patients. Twelve weeks after the procedure, patients had statistical improvements in symptoms by DeMeester score, increase in LES pressure and length, and reduced esophageal acid exposure. Average procedure time was 30 minutes. One patient in the series was oversedated and required endotracheal intubation. Another patient experienced a perforation requiring surgical closure. This event was recently duplicated in another report.[16]

The first multicenter study was an uncontrolled trial.[17] The end points of this investigation were a reduction of heartburn symptom scores by greater than 50% and antisecretory medication use to less than 4 doses per month. Ultimately, only 47% of the enrolled patients achieved this primary end point under the intention to