

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Endoscopic Treatment Strategies for Reflux Disease

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G&H Is there a specific set of GERD patients who are optimal candidates for endoscopic treatment?

RR Endoscopic treatments for gastroesophageal reflux disease (GERD) patients have been developed as an alternative to long-term use of medical therapy as well as, potentially, to surgical intervention, which is considerably more invasive. The ideal candidate for endoscopic treatment may get response from medical therapy but does not feel it fully addresses the symptoms and is either unwilling or unable to proceed to surgical therapy.

Patients receiving endoscopic therapy should have small and relatively insignificant, if any, hiatal hernias because large-hernia patients are not candidates for endoscopic treatment as it is currently performed. If a patient has severe erosive esophagitis where effective acid control is critical, endoscopic treatment is not the best primary therapy but it may serve as an excellent add-in to improve the efficacy of medical therapy with proton pump inhibitors (PPIs). Some GERD patients have on-going regurgitation despite relief of pyrosis with acid suppression, and endoscopic treatment may be of benefit to control this chronic bother. In short, from the experience seen so far, the best candidates for endoscopic GERD treatment are those with mild disease who do respond to acid suppression. Continued investigation is needed on the role of endoscopic therapies for other clinical situations.

G&H Can endoscopic therapy impart added benefit in patients with extraesophageal symptoms of GERD?

RR Patients with extra- or supraesophageal GERD symptoms generally evince a multifactorial etiology. Regardless of therapy, it may be somewhat difficult to address all of the causes and control all of their symptoms. However, when GERD plays a role, there has been some benefit seen with aggressive medical therapy as well as surgical therapy. There is only a small amount of data to suggest that endoscopic therapy may be of benefit as well. I believe this is an area for future research, not likely as a replacement for medical therapy, but rather as an adjunct. Esophageal impedance testing will allow us to examine whether both acid and nonacid reflux episodes are controlled by endoscopic therapy in patients with extraesophageal symptoms of GERD.

G&H Could you describe the endoscopic procedures that are currently in use for the treatment of GERD?

RR We typically divide the endoscopic treatments for GERD into 3 broad categories: sewing and pleating (also known as plication), thermal energy delivery to the lower esophageal sphincter (LES) via radiofrequency source, and injection or implantation of a bulking agent into the area of the LES. Of those broad categories, we currently have available only 2 techniques. They are the EndoCinch (C. R. Bard) for endoscopic suturing, which allows for partial thickness plication, and the full-thickness Plicator (NDO Surgical) which performs serosa-to-serosa apposition. These procedures are designed to control symptoms by altering the mechanics or anatomy of the gastroesophageal junction and cardia, with a goal to reduce acid exposure in the esophagus and to potentially provide healing of the esophageal mucosa. They can be done as repeat procedures and can be performed in under an hour as outpatient surgery.

The EndoCinch has been in use the longest of the endoscopic treatments. In this procedure, the endoscopist stitches 2–4 pleats just below the gastroesophageal junction, each of which requires approximately 10 to 15 minutes to create. The initial result should allow for control of heartburn and regurgitation. In the earlier studies, approximately two thirds of patients undergoing the procedure were off PPI therapy at 12 months. However, at 2 or more years, less than 15–20% of patients are able to stay off of PPI therapy and still remain free of GERD symptoms. This is for the most part a problem of the durability of the superficial stitch. Further, though the procedure does improve quality of life and reduce transient LES relaxation events, it has not proven effective for healing erosive esophagitis and it only normalized esophageal pH in about one third of patients. There have been 3 sham-controlled trials of the EndoCinch, and all have shown a very modest effect in normalizing or changing the pH in the cohorts of treated subjects. In 2 of the studies, there was a small advantage to the treated group over sham in short-term follow-up evaluating the need for postprocedural antisecretory medication, whereas in the third study, with a 1-year follow-up, there was no difference in this outcome between the treated and sham groups. Overall, the EndoCinch is a promising procedure, but there are problems with its durability. It does appear to be the safest endoscopic technique. There have been no deaths associated with its use and only a few, mostly minor, adverse events.

The full-thickness NDO Plicator system incorporates a sophisticated endoscopic accessory, through the center of which a 6-mm endoscope is passed and used as the optical system. The instrument is passed into the stomach over a guidewire, then retroflexed up to the top of the stomach. The Y-shaped arms are opened and a tissue grasper emerges, engages the cardia about 1 cm below the gastroesophageal junction, pulls the tissue in, and closes it down to create a pleated area at the top of the stomach by delivering a preformed nylon monofilament suture implant. In the initial trial of this procedure, approximately 80% of patients were off medical therapy at 6 months, 70% at 1 year, and 63% at 3 years. Thus, the durability of this procedure was shown to be viable. It positively affected patient quality of life but only normalized esophageal pH in about one third of patients. Interestingly, the Plicator did not lengthen the LES or increase its tone, and it was not effective in the healing of erosive esophagitis. No testing was done for effect on transient LES relaxation. Its safety profile was relatively good although there were several important events: pneumothorax and pneumoperitoneum, as well as 1 gastric perforation. All of these adverse events were associated with the initial Plicator model, which did not have a covering

over the exposed metal parts and which used an overtube. These design features were corrected with the next generation of the device, and there have been no major problems with it since then.

In October of 2006, a sham-controlled trial of the Plicator procedure was published in *Gastroenterology*. Patients with mild reflux disease (N=159) were randomized to either plication or a sham procedure. Of the plicated patients, approximately 62% achieved the targeted endpoint of 50% or greater reduction in their heartburn score, compared to only 20% in the sham group. In the intention-to-treat (ITT) analysis, 50% versus 18.5% achieved the endpoint, respectively. Looking at PPI use per-protocol, 59% of the Plicator patients stopped PPI therapy, compared to 26% in the sham group, and this remained significant in the ITT analysis. In addition, median esophageal pH fell from 11 to 7 in the Plicator group but did not change in the sham group. These measures were at 3-month follow-up. This was the first randomized, sham-controlled endoscopic treatment trial that clearly demonstrated improvement in objective (pH) outcomes. There were no major adverse events in this trial. Longer-term data will be presented at the 2007 Digestive Disease Week meeting. This treatment appears to have a real potential to be of benefit for GERD patients.

An important point to make with all of these trials is that they represent data from learning-curve procedures in small numbers of patients. With greater endoscopist experience and optimization of the techniques and instruments, we hope to improve overall results. A small study of the Plicator instrument in Germany examined the practice of administering 2 pleats rather than 1, and results improved significantly. However, more data is needed to confirm these findings.

G&H Are there new procedures and devices currently under investigation?

RR Along with optimization of the current procedures, investigators are looking at other full-thickness plication devices. New equipment is under development at a variety of device companies. One study of the device formerly known as Esophyx (EndoGastric Solutions), which is currently available for use in the European Union, followed 17 patients who were referred for surgery but underwent the endoscopic procedure instead. At 3-months follow-up, 15 of the 17 were off PPI therapy, and pH had been normalized in 10 of 11 patients, which is very impressive. We await publication of data regarding a remodeled version of the device, which has the potential to take endoscopic procedures for GERD to a new level of efficacy.

G&H Are there differences amongst these procedures in terms of patient convenience and recovery time?

RR The differences among the various procedures are minimal. Patients undergoing full-thickness plication tend to feel more chest pain than those receiving partial-thickness plication. However, all patients recover well from their moderate sedation, and any associated chest pain is transient.

These are all outpatient procedures that can be performed in a hospital endoscopy unit or an ambulatory surgical center. They are typically done with moderate sedation, or with propofol if needed, and last under an hour. They do not require general anesthesia. Dietary modification consists of 1 day of soft food and is then advanced as tolerated. Pain medicines are generally not necessary after the first several days, and most patients are generally back at work, performing their normal tasks, within 24 hours. By contrast, patients undergoing surgical therapy are in the hospital overnight and require at least 2 weeks to fully recover.

G&H What long-term data are available in these patients?

RR Unfortunately, there is very little quality long-term data in these patients. When available, there appears to be a decline in effect over time; however, there have been few long-term outcomes reported. There should be attention placed on improving the techniques for better clinical outcomes. One study that has been proposed by the NDO Plicator group is to re-treat and study patients who did not show durable benefit from the initial plication, but no systematic data have yet been collected.

One of the real shortcomings of all endoscopic GERD therapies is that long-term follow-up studies have been underfunded. Although 10,000–12,000 pro-

cedures have been performed, efficacy and patient data are available in only a minority of them and that causes problems in trying to interpret outcomes. We have no real data on which of these patients have severely abnormal pH profiles, larger hiatal hernias, or atypical symptoms. Other patient populations that need to be studied separately are failed surgical patients, nonsurgical and medical candidates such as pregnant women, pediatric patients who may face lifelong acid suppression with PPIs, and postbariatric-surgery patients.

G&H What cost effectiveness data are available for endoscopic GERD procedures?

RR With endoscopic therapy for GERD, it was once thought that if a durable effect could be achieved for 3 years, the procedure would be cost-effective when compared with surgery or medical therapy. This calculation will change with the advent of cheaper over-the-counter PPIs. Again, better outcomes data are needed to completely factor costs and develop a logical decision model for utilizing endoscopic therapies in everyday patient treatment.

Suggested Reading

Pleskow D, Rothstein R, Kozarek R, et al. Endoscopic full-thickness plication for the treatment of GERD: long-term multicenter results. *Surg Endosc*. 2006 Dec 16; [Epub ahead of print].

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