

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Endoscopic Procedures in the Treatment of GERD

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G&H What are the different types of endoscopic procedures available for the treatment of gastroesophageal reflux disease?

WH Endoscopic antireflux treatments, either using an endoscope or with the assistance of an endoscope, have been in clinical use since 2000. Currently, there are 5 devices approved by the US Food and Drug Administration: The Stretta System (Curon Medical), the EndoCinch Suturing System (CR Bard), the Plicator System (NDO Surgical), Gatekeeper (Medtronic), and Enteryx Injection Therapy (Boston Scientific).

The 5 devices that have been developed employ a few different approaches. The Stretta instrument applies radiofrequency thermal energy to the lower esophagus. The Plicator and EndoCinch systems use a sewing mechanism to stitch plications in the proximal fundus of the stomach to prevent reflux. The Enteryx and Gatekeeper systems inject a polymer substance to bulk the distal esophagus. Thus, all of these instruments aim to either reinforce the sphincter or prevent gastric contents from entering the esophagus by forming a mechanical barrier.

G&H What have studies reported about the efficacy of these procedures in this disease setting?

WH Numerous studies of these instruments have been conducted, but most have been open label. Patients with gastroesophageal reflux disease (GERD) have been involved in studies without randomization or sham treatment. They have undergone treatment and have then been followed for various periods to assess results. There have been only 2 blinded, randomized, controlled clinical trials. The first of these studies, published in 2003, evaluated the Stretta radiofrequency procedure.

In this study, patients were randomized to undergo this procedure or to a sham control arm. The study lasted for 6 months, at which point patients in the control group were offered treatments with Stretta. Unfortunately, the short study duration led to less rigorous data than would have resulted if the control group had been maintained for a full year. Patient symptoms and need for antireflux medications were reduced. The second study, published in 2005, evaluated the Enteryx system in a randomized controlled trial from multiple centers in Europe. This study demonstrated efficacy by decreasing or eliminate proton pump inhibitor (PPI) use according to the study goals (described below).

All of the other reports or results from the endoscopic antireflux techniques have been either anecdotal or based on open-label studies. Randomized trials are crucial for evaluating the potential benefit of these techniques in preventing reflux because the placebo response rate may be as high as 50–60%. It is essential to have a placebo control group in order to clearly determine whether these therapies are truly beneficial.

The majority of studies have shown that these techniques reduce patients' symptoms of heartburn and improve quality of life, and some studies have shown a reduction in acid reflux. However, on most reports these techniques have not normalized acid reflux. Patients have become less symptomatic and the need for antacid medication has been reduced or eliminated. For example, in the clinical trial evaluating Enteryx, 2 endpoints were measured: a greater than 50% reduction in the use of medication or elimination of medication in greater than 50% of patients. In this study, the majority of patients were able to stop medication or reduce antacid use to this degree. In a recent nonrandomized study published in abstract form, a small group of Enteryx patients followed for 36 months maintained these promising results.

Very few of the endoscopic reflux studies have shown improvement or elimination of reflux esophagitis. The benefits of these endoscopic antireflux procedures have been almost exclusively in terms of improvements in quality of life due to reduction in heartburn or eliminating or reducing antacid medication.

G&H Have these studies included all types of GERD patients or a selected subgroup?

WH The patients enrolled in these studies have generally encompassed a narrow subgroup of GERD patients. For example, patients have typically not had severe esophagitis or a hiatal hernia measuring more than 2 centimeters, whereas patients with severe GERD often have both significant esophagitis and larger hiatal hernia. In addition, patients have been stratified according to such parameters as their inability to completely relieve their symptoms following therapy with a PPI. This group has never been critically defined in the majority of studies.

In more recent studies, the patient groups that have been enrolled have experienced recurrent symptoms when antacid medication is stopped, a subgroup more clearly defined. However, many reports have included patients who have persistent symptoms on PPIs. These are not typical GERD sufferers. An abstract presented at the 2004 American Gastroenterological Association annual meeting indicated that at a center that has a high number of GERD patients, only one third would be candidates for antireflux therapy based on current study criteria. At our institution, this number would be closer to 25%. Thus, these instruments currently are applicable to a specialized patient subgroup and not to a wide array of patients with GERD.

G&H What side effects have been associated with these procedures in GERD studies so far?

WH Some procedures have been associated with significant morbidity and mortality. In a postmarketing study of the Stretta System, 3 fatalities were reported, and 5 patients experienced complications leading to death after treatment with Enteryx. In addition, other serious side effects have been observed with the use of these procedures such as chest pain, dysphagia, or bleeding. After the Enteryx procedure, approximately 90% of patients experience significant chest pain, sometimes for 2 weeks or more. These problems are not seen with antacid medication, which is the gold standard to which any new approach to GERD therapy must be compared. There may be some risks associated with medication, but mortality is not one of them.

G&H Might there be benefits to these procedures that have not yet been fully realized? In what setting might these procedures be appropriate?

WH There may be some benefits offered by these techniques that have not yet been fully appreciated. For example, in a recent study published in *Gastrointestinal Endoscopy* of the Gatekeeper system in which polymer

disks were inserted in the distal esophagus, there was no reduction in acid reflux measured in the distal esophagus by pH testing, but there was decreased acid reflux in the more proximal (upper) part of the esophagus. The improvement in symptoms observed in this study may have been due to a reduced quantity of reflux entering the upper part of the esophagus, which has been shown to be the more sensitive site for heartburn symptoms compared to the lower esophagus.

There is probably a role for these endoscopic reflux procedures, but I think it remains to be defined. It may be that endoscopy for GERD is applicable only to a small subgroup of patients or for specific situations. At the present time it seems necessary to learn more about these procedures within the confines of large randomized studies in order to determine whether they are associated with significant morbidity and whether the improvements they produce are reasonable long-term therapeutic results.

Patients with volume acid reflux may be appropriate candidates for these techniques. These are patients in whom the volume of reflux has not been reduced sufficiently with PPI medication. Fundoplication surgery has been around for decades and has been found to be effective for this group of patients. However, some patients with volume acid reflux who are not surgical candidates and do not respond to or cannot tolerate PPIs may benefit from an endoscopic procedure. Still, these procedures would need to show comparable or superior results.

Patients who do not want to take medication may also be candidates for an endoscopic procedure. However, these procedures often lead to a reduction, not an elimination of medication. A reduction in medication from 2 PPI tablets per day to 1 tablet per day does not seem to warrant the risks associated with these procedures.

G&H Is there any clear sense of how endoscopic antireflux treatments compare with standard PPI therapy for GERD?

WH No study has yet compared standard medical treatment with these endoscopic antireflux procedures. Such a study would require fairly specific profiles for the enrolled patients. For example, if a patient with GERD does not experience a benefit from PPI medication, it may be that the symptoms are refractory or it may be that the symptoms are not due to reflux at all. If there is some risk of mortality associated with any given treatment for GERD, it should be approached very cautiously, particularly since GERD is not a disorder generally associated with such outcome. The risk/benefit ratio of an endoscopic procedure might not favor an approach associated with potential severe side effects. As an example, the Stretta procedure, which uses radiofrequency ablation, produces

thermal lesions in the esophagus that appear to alter the tissue, making it less pliable. Recent studies now suggest that the sensory impulses from the distal esophagus are also ablated by this procedure so the patient may not experience heartburn, but reflux continues. Heartburn is a symptom that indicates an underlying problem in the distal esophagus and it may not be beneficial to eradicate heartburn symptoms without significantly eliminating the distal esophagus to acid exposure.

G&H Do endoscopic procedures offer a benefit in terms of cost-effectiveness in the treatment of GERD?

WH Endoscopic procedures for GERD may be more cost-effective if the need for medication is permanently eliminated. However, if the procedure needs to be repeated once or twice, the cost-effectiveness is diminished. A recent report found that 1–1.5 years after the EndoCinch system had been used in a group of patients, the majority of stitches had loosened or disappeared. Also, if a severe adverse event occurs that requires the patient being admitted to the intensive care unit, the potential savings of the procedure are immediately cancelled out.

G&H Might these instruments be effective in settings other than GERD?

WH Yes. For example, the Plicator is used to pull together the stomach folds and yield a fundoplication. There is interest among surgeons and gastroenterologists in potential application to other areas, for example, stomach bariatric surgery. However, in this setting the endoscopic procedure would need to be compared with the laparoscopic technique. Twenty years ago no one would have conceived of removing a gallbladder laparoscopically. Now nearly all cholecystectomies are done this way. In

the same manner, it may be that we will be surprised by the applications of these endoscopic procedures in coming years. However, appropriate randomized clinical trials must be conducted, over several years if necessary.

Suggested Reading

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