Treatment of Gastroesophageal Reflux Disease: Endoscopic Aspects

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GERD, endoscopic aspects · Radiofrequency energy · Injection techniques · Hydrogel prosthesis · Endoscopic suturing

Abstract
Gastroesophageal reflux disease (GERD) is a very common chronic disorder manifesting itself as heartburn, regurgitation, or dysphagia, possibly leading to esophagitis, Barrett’s esophagus and adenocarcinoma, and has a major impact on the patient’s quality of life. Both medical treatment and surgery are well-established methods with several limitations. Recently, three types of endoscopic methods in several modifications have been developed: (1) Radiofrequency therapy (Stretta procedure) is available both in Europe and USA and more than 5,000 patients have been treated to date. (2) Injection therapy requires the injection of bulking agents or implantation of bioprosthesis into the lower esophageal sphincter (LES) zone. Both Enteryx was withdrawn from the market in 2005, and Gatekeeper was suspended before FDA approval. (3) Suturing/plication therapy is based on the plication at the level of the LES, and most of all techniques resemble the principle of surgical treatment. Despite sophisticated technologies and promising short-term results, all these techniques are associated with inconsistencies, controversies, and relevant adverse affects. According to current practice, use of endoscopic methods is justifiable only as part of clinical trials. Many aspects, including commercial ones, will influence future developments in this area, which are difficult to predict.
A variety of endoscopic techniques for the treatment of GERD have been developed including the delivery of radiofrequency energy to the gastroesophageal junction, injection of bulking agents, or implantation of a bioprosthesis into the LES zone, and suture plications of the proximal fundic folds.

While apparently encouraging results have been achieved in the short term, several inconsistencies have emerged between the efficacy and objective parameters, and promising results were obtained over a period of about 6 months in only about two-thirds of patients. An optimal endoscopic technique should be effective, safe, and easy to master making it useful for most endoscopists [1].

Radiofrequency Energy

Monopolar radiofrequency devices use an active electrode and a dispersive electrode. The Stretta device is commercially available both in Europe and the USA. The principle of temperature-controlled radiofrequency energy has previously been used for a variety of other medical conditions (cardiac arrhythmias, tumor ablation, benign prostate hypertrophy). The radiofrequency energy is delivered through a flexible catheter and an inflatable balloon at the level of the gastroesophageal junction. Four needles deliver radiofrequency at several levels, causing molecular shortening of collagen fibers, activation of macrophages and fibroblasts, remodeling of the gastric cardia region with increased muscular wall thickness, and reduced tissue compliance (pig and canine models) [2].

Consequently, an increase in basal lower esophageal sphincter (LES) pressure, a decrease in the frequency of transient LES relaxation episodes, and improvement in gastric emptying have been reported.

Radiofrequency energy is delivered by a special catheter and energy generator containing one channel per needle for a total of 4 channels, an irrigation pump, and a temperature control feedback system. If the endpoints exceed a particular level, the generator will automatically shut off that needle. Needles are made of nickel-titanium and feature a thermocouple (electrical thermometer) at their tip and base. The Stretta procedure is usually performed under standard but conscious sedation (meperidine and midazolam at doses of up to a double or even more times higher than those used for colonoscopy).

A numerous list of mostly uncontrolled trials includes more than 5,000 patients treated. Triadafilopoulos et al. [3] reported the results of an initial US open-label study of radiofrequency delivery first to 47 (6 months) patients and subsequently to 118 patients (12-month follow-up). Significant improvement of heartburn symptoms and quality-of-life scores was documented. PPIs were completely eliminated in 70% of treated patients; however, there was no significant difference in patients with esophagitis. Post-hoc analysis showed that responders had a significant decrease in distal esophageal acid exposure compared to non-responders. Corley et al. [4] reported the first sham study demonstrating significant improvement of reflux symptoms and quality of life. However, neither PPI use nor acid exposure were affected significantly by experimental treatment. It is hypothesized that the favorable effects are more likely to be related in esophageal sensitivity, possibly caused by ablative denervation.

A plethora of adverse events have been described varying from self-limited to serious ones, and even death. Chest pain as the most typical adverse event appears in 1.7–100% patients. Other complications include fever, dysphagia, mucosal injury, submental swelling, vomiting, bleeding and mediastinitis. There were 3 deaths caused by sedation, esophageal leak, and aspiration.

Injection Techniques

Various injectable agents have been tested for bulking the gastroesophageal junction inspired by O’Connor et al. who injected Teflon paste into a canine esophagus. The same group of investigators consequently reported the first human experience with bovine dermal collagen. The immediate improvement reversed to pretreatment levels by 1 year. Four implantable products have been further tested in humans: polymethylmethacrylate microspheres (Plexiglas), polytetrafluoroethylene (Polytef), a hydrogel prosthesis (Gatekeeper), and an ethylene vinyl alcohol copolymer (EVOH) with tantalum dissolved in dimethyl sulfoxide (DMSO – Enteryx). The last two compounds became available, but Enteryx was withdrawn from the market by the manufacturer in 2005 because of complicating transmural injections; similarly, the development of Gatekeeper was suspended in 2005.

With this combined endoscopic and radiologic technique, endoscopic view helps to select the appropriate injection site whereas fluoroscopy serves to monitor the depth of injection to avoid intravascular or extraluminal administration. The visualization under fluoroscopy is due to micronized tantalum powder. The injection sys-
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The first attempts in this area were reported 20 years ago. To date, two basic systems have been developed (two devices approved by the Food and Drug Administration (FDA) and a third one not yet approved is available as an investigational device). The Bard EndoCinch instrument consists of a suturing system, overtube, needle pusher, knot pusher, and a suture cutter. The principle of this technique is based on the creation of a plication below the Z-line at the level of the LES to create a valve mechanism at the gastroesophageal junction. The endoscope with an attached sewing capsule is placed into the overtube and introduced down the esophagus. The stitching is done with the help of suction and needle penetration. Sedation

The Gatekeeper

The principle of this technique consists of the placement of 3–6 prostheses into the submucosal layer of the esophagus at the squamocolumnar junction under endoscopic guidance. The components of the delivery system involve a 16-mm overtube, a prosthesis delivery system (needle, dilator, sheath), and a pushrod assembly. An injection needle is advanced using a dedicated sheath of the overtube, and saline is injected into submucosal tissue through a slot at the distal end of the overtube forming a submucosal cushion. The prosthesis is then delivered and advanced into the saline-expanded space. The overtube is then rotated to unable to introduce another prosthesis at a different site. On average, 4 prostheses are delivered over 26.6 min [9].

Concerning the mode of action studied both in animal models and humans, Gatekeeper insertion resulted in an increase in LES pressure and gastric yield pressure in response to stomach inflation, but the effect disappeared within several months. Necropsy inspection of the esophagus showed minimal fibrosis around the prostheses [10].

A study by Fockens et al. [9] included 68 patients. The primary endpoints, GERD-HRQL and SF-36 score improved significantly; surprisingly, median acid exposure time was not improved at 3 months, but was improved at 6 months. Data on pharmacotherapy were not collected systematically and the information available is considered unreliable. As regards safety issues, 15% of patients reported usually mild adverse effects with only 2 patients requiring hospitalization for pharyngeal perforation and for intractable nausea [11].

Endoscopic Suturing

The principle of this technique consists of the placement of 3–6 prostheses into the submucosal layer of the esophagus at the squamocolumnar junction leading possibly to fewer reflux events. Direct morphological evidence was reported in human study evaluating implants injected prior to scheduled esophagectomy. Thirty of 34 implants were correctly placed, but 4 were located either subserosally or externally to the gastroesophageal junction [5].

Similar to other endoscopic techniques on GERD, many studies have been published, but controlled designs are scarce. In a cohort international multicenter study by Johnson et al. [6], patients from 8 sites were enrolled during a 6-month period. 84% of patients achieved the primary endpoint of \( \geq 50\% \) decrease in PPI dosage at 6 months, and 74% reported their completed elimination. GERD symptoms, quality-of-life scores, and esophageal acid exposure improved significantly as well. Recently, several controlled clinical trials were completed. A European sham-controlled multicenter trial included 64 patients. The primary endpoint was a \( \geq 50\% \) reduction in PPI use, secondary outcomes involved \( \geq 50\% \) improvement of symptoms, and the proportion of patients requiring re-treatment. PPI use was reduced in 78% of the Enteryx group vs. 53% of sham-treated patients at 3 months. GERD manifestations improved by a median of 63% in the active group vs. 25% in the sham group; the change in quality-of-life score also differed significantly. There was no difference in esophageal acid exposure. Further outcomes are not analyzed because the study was unblinded not representing the original randomized scheme [7].

Concerning safety issues, chest pain lasting several days appeared in a majority of patients, and dysphagia lasting weeks to months in up to 28% was reported; transient fever was also rather frequent. Serious adverse effects include esophageal abscess, pneumomediastinum, pericarditis, and aortoenteric fistulas including 5 deaths. Several patients required interventional treatment (chest drainage, esophageal dilation) [8]. The severity of these reported side effects was the reason why the manufacturer withdrew Enteryx from the market on September 22, 2005.

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required for this procedures varies (59% conscious sedation, 27% propofol, 14% general anesthesia) as does median procedure time (33–68 min). The mode of action was tested both in animal models and humans. According to Tam et al. [12], gastroplication resulted in a significant increase in mean postprandial LES pressure without changing fasting basal LES pressure and, similarly, median transient LES relaxation frequency and acid exposure time decreased significantly. According to another study, gastroplication may cause a decrease in acid sensitivity [12, 13].

Inconsistencies among the different studies regarding the number and position of plications remain. The main concern is the durability of effect, which may depend on the depth of stitches involving the muscular layer in the plication. Potential advantages of the sewing devices are that the method can be repeated, it may be relieved if necessary (dysphagia), and it does not rule out surgery if needed. The above US multicenter trial included 64 patients, and 52% linear and 48% circumferential plications were performed. Treatment success was defined as a decrease in heartburn severity and a reduction in the use of antireflux medications. The success was achieved in 58.8% (per protocol analysis) and 62%, respectively. Mean acid exposure time decreased, but no changes were noted in LES pressure or grade of esophagitis, though [14].

A large number of uncontrolled studies have been subsequently published, including the series from Asian countries at DDW 2006, with significant improvement of symptoms and acid exposure [11].

Several sham-controlled clinical trials have been published in abstract form. In a study by Rothstein et al. [15], there were significant differences in heartburn frequency, acid exposure time, and reduction of antireflux medication at 3 months. The outcomes were different in another study, which did not demonstrate the superiority of gastroplication. On the other hand, preliminary results of a third trial did show some improvement at 3 months [15–17].

Several trials were designed to compare gastroplication and antireflux surgery. In one of these [18], less medication use was reported in the surgery group at a mean follow-up of 8 months.

Adverse events requiring hospitalization or interventional treatment, involving mediastinitis treated by antibiotics, bleeding, and aspiration pneumonia, are scarce. Most events are transient and include pharyngitis, chest pain, vomiting, and pain.

The Endoscopic Plication System creates a full-thickness, through-the-wall plication of the proximal stomach. Currently, a second-generation system without an overtube involves a small pediatric endoscope for control of the operating field from retroflexion. The NDO instrument deploys a single-use, preformed suture-based implant. The instrument was tested in a porcine model and all devices are still under development. After the promising results of a pilot study, Pleskow et al. [19] presented the results of a North American multicenter trial. The study proved the procedure was successful in all measured outcomes. Serious adverse effects were reported in 6 patients, including dyspnea, pneumothorax, pneumoperitoneum, and gastric tear requiring laparotomy in 1 case.

Endoscopic treatment of GERD is enormously attractive, and several techniques are currently available. Nevertheless, positive results have been obtained in only approximately two-thirds of patients with a median follow-up of 6 months; this proportion will presumably further decrease after a longer period of time. The main inconsistency is the difference between the efficacy of treatment in terms of improvement of manifestations and quality of life, and the lack of improvement of objective parameters such as LES pressure and esophageal acid exposure. Obvious explanations include the heterogeneity of patients, placebo effect in uncontrolled studies, limited knowledge about the mode of action, and diversity of outcomes. The endoscopic techniques suffer from numerous technical shortcomings whose elimination could possibly improve both the efficacy and duration of the therapeutic effect. Particularly in preliminary studies, the results were overshadowed by numerous serious adverse effects resulting from precipitous uncontrolled development. The obvious question is whether the benefits of endoscopic treatment are worth the risks. This could only be clarified if the risks of surgical procedures and acid suppression lasting for decades will be precisely analyzed and controlled trials with representative outcomes on homogeneous groups of patients performed [20].

References


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