Editorial

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Endolumenal therapies for gastroesophageal reflux disease: are they dead?

Jonathan P. Pearl, Jeffrey M. Marks

Department of Surgery, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Since first approved for clinical use in 2000 endolumenal therapies for gastroesophageal reflux have filled a desirable niche. Patients and endoscopists alike were allured by the prospect of an outpatient procedure without skin incisions that would alleviate reflux symptoms. However, the introduction of endolumenal therapies for GERD preceded sound clinical data supporting their use. Some of the devices were either ineffective or caused an inordinate number of complications.

Because of the early shortcomings of certain endolumenal therapies for GERD this type of therapy is now being scrutinized closely. Overwhelmingly positive data have been called for to support their use. In fact, endolumenal therapies are at risk of being held to a higher standard than either medical or surgical management of GERD. We must recall that our current gold standard, the laparoscopic Nissen fundoplication, provides symptom relief in 85% of patients, but about 1 in 20 experience prolonged dysphagia.

There has been a series of specific criticisms of endolumenal therapies for GERD. Some commentators note the lack of sham controls in published randomized controlled trials [1], which might be critical in a disease such as reflux where a 25% to 50% placebo response is routinely reported. Additionally, the efficacy and safety of some therapies has been questioned, with the recent withdrawal of one of the prosthetic barrier devices.

In order for endolumenal therapies to gain a foothold, realistic endpoints should be met. Requiring greater than 90% efficacy is unnecessary, but a durable barrier to reflux and symptom relief in 75% of patients is realistic and achievable. Herein, we review the extant literature concerning endolumenal therapies for GERD and look toward the future in this burgeoning field.

Correspondence to: Jeffrey M. Marks

Suturing devices

Akin to laparoscopic Nissen fundoplication, endolumenal suturing devices serve to alter the hiatal anatomy in order to prevent reflux. Systems for both mucosal apposition and full thickness sutures have been introduced, with more durable results achieved by full thickness gastric plication.

Mucosal plication device

The EndoCinch plication device (CR Bard, Inc, Murray Hill, NY) creates an internal mucosa-to-mucosa plication of the stomach. Using a standard endoscope outfitted with the device at its tip, the tissue is drawn into the suturing chamber by suction, and two sutures are placed. The knots are formed extracorporally and advanced to the gastric mucosa.

Chen et al. performed a long-term, multi-center study of 85 subjects [2]. Over 50% of patients showed symptom resolution at 12 and 24 months, and 73% of available patients reported reduction in PPI use. There was a statistically significant decline in esophageal acid exposure by pH probe, but no repeat endoscopy was employed to examine the plication.

In a study by Schiefke et al. 70 PPI-dependent patients received EndoCinch and were followed for 18 months [3]. A total of 6% of patients completely stopped PPIs, and 24% reported a greater than 50% reduction in PPI use. At long term follow up, 42% of sutures were intact upon endoscopic examination.

Another report by Abou-Rebyeh et al. documented the long term results of 43 procedures in 38 patients [4]. The 2-month data were encouraging with significant reduction in acid exposure, but all 38 patients were considered failures at 12 months. All plications were disrupted, and only 20% of patients reported diminution of PPI requirement.

While some of the short term results are promising, the long term results are bleak. The durability of a

mucosa-to-mucosa apposition is tenuous, as documented in the recent long term studies. Most authorities agree that technical refinements are necessary before the EndoCinch can be effectively used for gastroplication.

Full-thickness plication system

The NDO Endoscopic Plication System (NDO Surgical, Inc, Mansfield, MA) performs serosa-to-serosa apposition of the stomach just distal to the esophagogastric junction. The reusable device includes a suturing mechanism at its tip and a channel for passage of a small bore endoscope for visualization. The single-use suturing implant uses pre-tied polypropylene sutures with polytetrafluoroethylene bolsters. The instrument is passed with the aid of an endoscopically placed guide wire and retroflexed for deployment near the esophagogastric junction. A proprietary retraction device selects the tissue for plication before deploying the sutures with a turn of the handle.

In an abstract, Haber et al. reported the 12 month efficacy in 36 patients using a second-generation, reduced-diameter Plicator [5]. Of the 36 patients, 80% had reduced or ceased PPI usage, and 73% had objective findings from pH studies of reduced distal esophageal acid exposure.

Lin and colleagues published their findings of 10 complicated reflux patients in abstract form [6]. At short term follow-up 8 patients had reduced PPI usage, 5 of whom had entirely discontinued medication. Three patients had completely normal pH studies at 2 months.

Pleskow et al. described 12-month follow up of an open label, multi-center trial in an abstract [7]. A total of 64 patients underwent plication, and 40 of them used no PPIs after one year. There was a significant reduction in median GERD symptom scores, and 30% of patients had normal pH studies.

Despite the small sample sizes, the data are compelling for the NDO device. The full thickness apposition of tissue adheres to time-honored surgical principles, and the results are heartening. Further long-term and sham-controlled studies are needed before widespread application of this device.

Injectable prosthetics

Injectable endolumenal prosthetics aim to add bulk to the distal esophagus, but the clinical results have been discouraging. Concerns for patient safety incurred disfavor for this class of agents, and both have been voluntarily withdrawn from the market.

Gatekeeper

The Gatekeeper Reflux Repair System (Medtronic, Inc, Minneapolis, MN) alters esophagogastric junction anatomy in order to restrict the aperture for reflux. A saline lift is performed above the squamocolumnar junction, and a biocompatible cylindrical prosthetic comprised of polyacrylonitrite hydrogel is placed in the submucosa. The prosthetic subsequently enlarges with hydration, thereby impeding gastroesophageal reflux.

Cicala and colleagues performed an observational study in 9 patients [8]. After 6 months, pH variables were not significantly ameliorated, but all patients reported improvement in GERD health related quality of life scores. The study was underpowered to draw conclusions.

Fockens and colleagues published a prospective, nonrandomized, open label study in 67 patients [9]. There was a significant increase in lower esophageal pressure and a significant decrease in distal esophageal acid exposure. Most patients reported improvement in their quality of life, and over 70% of the prostheses were retained at 6 months. There were 2 significant complications of the procedure: one patient sustained a pharyngeal perforation which was managed nonoperatively, and another experienced intractable post-prandial nausea necessitating removal of the prosthetic.

The manufacturer has since withdrawn the Gatekeeper system from the market.

Enteryx

For augmentation of the lower esophageal sphincter, the Enteryx (Boston Scientific Corp, Natick, MA) system uses a biocompatible, non-biodegradable polymer. The solution contains the liquid polymer and radiopaque material to gauge the depth of injection. A circumferential injection of the polymer is performed, and its subsequent solidification tightens the esophagogastric junction.

Multiple recent studies employing the Enteryx system have been published. Of note, Deviere and colleagues described the first sham-controlled trial with Enteryx in 2005 [10]. Of the 64 patients, 83% reduced PPI use by 50%, and 68% had discontinued PPIs. However, in the sham arm, 53% had halved their PPI use, and 40% discontinued PPIs. There was no objective improvement in pH values.

Schumacher et al. published a prospective, multicenter, open label study to assess the safety and efficacy of Enteryx [11]. A total of 93 patients were enrolled, and 74 were evaluable at 6 months. There was subjective improvement in quality of life scores, and 65% had eliminated PPI use. There was no significant change in objective pH data, and over 75% of patients experienced post-procedural chest pain.

The most influential reports documented the safety profile of Enteryx. Noh and colleagues reported a case of pneumomediastinum [12], and Tintillier et al. decribed a death from a paraesophageal abscess [13]. Wong et al. documented two patients with chest pain, fever, leukocytosis, and pleural effusions [14]. In a report to the FDA, the manufacturer detailed a single death from exsanguination resulting from injection of the polymer into the aorta [15]. Prompted by concerns for safety, the manufacturer voluntarily recalled Enteryx injection systems in September 2005.

Radiofrequency energy

The temperature-controlled endoscopic delivery of radiofrequency energy is termed the Stretta (Curon Medical Inc, Sunnyvale, CA) procedure. An inflatable balloon is equipped with 4 needles that penetrate the submucosa and deliver a controlled dose of thermal energy. The delivery is performed at multiple locations in the distal esophagus as well as the gastric cardia.

The largest study of radiofrequency administration for GERD is the multicenter, prospective Stretta registry [16]. Wolfsen and Richards published their results from 558 patients who participated in the trial. There was significant improvement in GERD symptoms in 77% of the patients. The procedure resulted in a rapid onset of symptom relief, and in those patients deemed responders, the salutary effects persisted beyond one year.

Lufti and colleagues published a prospective, single center, open label study of 77 patients with more than 6 months of follow-up [17]. Over 75% of participants responded to a mailed questionnaire. A total of 79% of those reported improvement in GERD symptoms, and half denied medication requirement. There was a significant enhancement in GERD-related quality of life, and pH studies at 6 months demonstrated significant remediation in acid exposure.

Another multicenter, prospective, open label study from Triadafilopoulos and colleagues included 118 patients, of which 94 were available for 12 month follow up [18]. There was significant symptom relief, and PPI use declined from 81% to 33%. At 6 months, there was a statistically significant improvement in pH data.

As a whole, the data from Stretta are compelling. This simple procedure seems to offer subjective improvement in GERD symptoms, possibly even providing a barrier to distal esophageal acid exposure, with a paucity of side effects.

Conclusions

Endolumenal therapies for GERD are not dead, rather still in evolution. Favorable results have been reported with some therapeutic modalities, and others appropriately relegated for safety and efficacy concerns. After the fallout from the first generation of endolumenal therapies we are left with the Stretta and NDO Plicator. Both the Stretta and NDO Plicator appear to meet the criteria of durable relief of reflux symptoms and normalization of distal esophageal acid exposure in 75% of patient. These are realistic achievements favoring application of endolumenal therapies in the proper context.

At the time of this printing, the manufacturer of Stretta, Curon Medical, has made formal plans to dissolve the company, declaring Chapter 7 Bankruptcy. The company is in the process of selling the rights for continued manufacturing of its products. We are hopeful that this won't interrupt the clinical application of this useful product.

Endolumenal therapies for GERD are not a panacea, and the indications are still in flux. At present GERD is considered a benign condition remediable with pharmacotherapy. However, the long-term effects of acid suppression are unknown, and someday an endolumenal approach may be preferred over pharmocotherapy. Even in the best of hands fundoplication provides an imperfect barrier to reflux with its attendant profile of side effects. Endolumenal therapy may be the bridge between pharmacotherapy and surgery, safely providing a durable barrier to reflux in the majority of patients who wish to discontinue medication but are not yet ready for an operation. Additionally, endolumenal therapy might be offered post-surgical patients whose symptoms persist or a priori to patients who want to minimize their risk of side effects knowing the might be only a 75% chance of efficacy.

We should not abandon endolumenal therapy for GERD. Experience and technological advances will certainly lead to improved outcomes and appropriate indications. Furthermore we should avoid succumbing to shortsightedness, but look to the future of endoscopic surgery. Reasonable successes in treating GERD could foster endolumenal opportunities in other facets of gastrointestinal surgery. Endolumenal bariatric procedures are not beyond imagination, and the instruments for today's (or next year's) treatment of GERD might segue into tomorrow's instruments for translumenal endoscopic surgery.

References

1. Hogan WJ (2006) Clinical trials evaluating endoscopic GERD treatments: is it time for a moratorium on the clinical use of these procedures? Am J Gastroenterol 101: 437–439
2. Chen YK, Raijman I, Ben-Menachem T, Starpoli AA, Liu J, Pazwash H, Weiland S, Shahrier M, Fortajada E, Saltzman JR, Carr-Locke DL (2005) Long-term outcomes of endoluminal gastroplication: a U.S. multicenter trial. Gastrointest Endosc 61: 659–667
3. Schiefke I, Zabel-Langhennig A, Neumann S, Feisthammel J, Moessner J, Caca K (2005) Long term failure of endoscopic gastroplication (EndoCinch). Gut 54: 752–758
4. Abou-Rebyeh H, Hoepffner N, Rosch T, Osmanoglou E, Haneke JH, Hintze RE, Wiedenmann B, Monnikes H (2005) Long-term failure of endoscopic suturing in the treatment of gastroesophageal reflux: a prospective follow-up study. Endoscopy 37: 213–265
5. Haber G, Sakai P, Moura E, Maluf-Filho F, Pleskow D, Lembo A (2005) The Plicator procedure for the treatment of GERD**:** 12-month multicenter results. Gastrointest Endosc 61: AB17
6. Lin E, Smith CD, Sedghi S (2005) Objective improvements following full thickness gastric cardia plication for complicated GERD. Surg Endosc 20: S040
7. Pleskow D, Rothstein R, Lo S, Hawes R, Kozarek R, Haber G, et al. (2005) Endoscopic full-thickness placation for the treatment of GERD: 12-month follow-up for the North American open-label trial. Gastrointest Endosc 61: 643–698
8. Cicala M, Gabbrielli A, Emerenziani S, Guarino MP, Ribolsi M, Caviglia R, Costamagna G (2005) Effect of endoscopic augmentation of the lower oesophageal sphincter (Gatekeeper reflux repair system) on intraoesophageal dynamic characteristics of acid reflux. Gut 54: 183–186
9. Fockens P, Bruno MJ, Gabbrielli A, Odegaard S, Hatlebakk J, Allescher HD, Rosch T, Rhodes M, Bastid C, Rey J, Boyer J, Muehldorffer S, van den Hombergh U, Costamagna G (2004) Endoscopic augmentation of the lower esophageal sphincter for

the treatment of gastroesophageal reflux disease: multicenter study of the Gatekeeper Reflux Repair. System. Endoscopy 36: 682–689
10. Deviere J, Costamagna G, Neuhaus H, Voderholzer W, Louis H, Tringali A, Marchese M, Fiedler T, Darb-Esfahani P, Schumacher B (2005) Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial. Gastroenterology 128: 532–540
11. Schumacher B, Neuhaus H, Ortner M, Laugier R, Benson M, Boyer J, Ponchon T, Hagenmuller F, Grimaud JC, Rampal P, Rey JF, Fuchs KH, Allgaier HP, Hochberger J, Stein HJ, Armengol JA, Siersema PD, Deviere J (2005) Reduced medication dependency and improved symptoms and quality of life 12 months after Enteryx implantation for gastroesophageal reflux. J Clin Gastroenterol 39: 212–219
12. Noh KW, Loeb DS, Stockland A, Achem SR (2005) Pneumomediastinum following Enteryx injection for the treatment of gastroesophageal reflux disease. Am J Gastroenterol 100: 723–726
13. Tintillier M, Chaput A, Kirch L, Martinet JP, Pochet JM, Cuvelier C (2004) Esophageal abscess complicating endoscopic treatment of refractory gastroesophageal reflux disease by Enteryx injection: a first case report. Am J Gastroenterol 99: 1856–1858
14. Wong RF, Davis TV, Peterson KA (2005) Complications involving the mediastinum after injection of Enteryx for GERD. Gastrointest Endosc 61: 753–756
15. FDA preliminary public health notification: recall of Boston Scientific Enteryx procedure kits and Enteryx injector single packs for treatment of gastroesophageal reflux disease (GERD). http://www.fda.gov/cdrh/safety/101405-enteryx.html. Accessed October 25, 2006
16. Wolfsen HC, Richards WO (2002) The Stretta procedure for the treatment of GERD: a registry of 558 patients. J Laparoendosc Adv Surg Tech A 12(6): 395–402
17. Lutfi RE, Torquati A, Kaiser J, Holzman M, Richards WO (2005) Three year's experience with the Stretta procedure: did it really make a difference? Surg Endosc 19: 289–295
18. Triadafilopoulos G, DiBaise JK, Nostrant TT, Stollman NH, Anderson PK, Wolfe MM, Rothstein RI, et al. (2002) The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. Gastrointest Endosc 55: 149–156