RAPID COMMUNICATION

Nonresorbable Copolymer Implantation for Gastroesophageal Reflux Disease: A Randomized Sham-Controlled Multicenter Trial

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Background & Aims: **This aim was to determine whether endoscopic implantation of a biocompatible nonresorbable copolymer (Enteryx; Boston Scientific Corp, Natick, MA) is a more effective therapy for gastroesophageal reflux disease (GERD) than a sham procedure.** ***Methods:*** **In a randomized, single-blind, prospective, multicenter clinical trial, 64 patients with GERD were enrolled whose symptoms were well controlled by proton pump inhibitor (PPI) therapy and rapidly recurred after cessation of PPI therapy. Thirty-two patients were assigned to Enteryx implantation and 32 to a sham procedure consisting of standard upper endoscopy. Patients in both groups with unsatisfactory symptom relief after 3 months were eligible for re-treatment by Enteryx implantation. The primary study end point was ≥50% reduction in PPI use. Secondary end points included ≥50% improvement in GERD score and the proportion of patients not undergoing re-treatment procedure. Follow-up evaluations were performed at 3 and 6 months.** ***Results:*** **The percentage of Enteryx-treated patients achieving a ≥50% reduction in PPI use (81%) was greater than that of the sham group (53%), with a rate ratio of 1.52 (confidence interval [CI], 1.06–2.28; $P = .023$). A higher proportion of the Enteryx (68%) than sham group (41%) ceased PPI use completely (rate ratio, 1.67; CI, 1.03–2.80; $P = .033$). GERD health-related quality of life heartburn score improvement ≥50% was achieved by 67% of the Enteryx group versus 22% of the sham group (rate ratio, 3.05; CI, 1.55–6.33; $P < .001$). More Enteryx-treated (81%) than sham-treated (19%) patients did not undergo re-treatment (rate ratio, 4.33; CI, 2.23–9.29; $P < .001$).** ***Conclusions:*** **Enteryx implantation more effectively reduces PPI dependency and alleviates GERD symptoms than a sham procedure.**

Minimally invasive endoluminal procedures for gastroesophageal reflux disease (GERD) are designed to provide long-lasting symptom relief and abolish or lessen medication dependency.[1] Several endoluminal modalities have now been introduced into clinical practice.[2–6] Among these are lower esophageal sphincter augmentation via endoscopic implantation of a biocompatible nonresorbable copolymer (Enteryx; Boston Scientific Corp, Natick, MA).[7] The copolymer is injected as a nonviscous liquid and rapidly forms a spongy solid in situ. By 3–6 months, the implant has been shown to undergo fibrous encapsulation in a porcine model.[8] The durability of the implant for at least 3 years has been demonstrated by spiral computed tomography in a small clinical study.[9] Lower esophageal sphincter augmentation with Enteryx is believed to derive its effectiveness by modifying the distensibility and compliance at the cardioesophageal junction.[8]

Clinical results of Enteryx implantation have been favorable.[10,11] In 2 prospective multicenter cohort trials involving 178 total patients followed up to 12 months, the procedure reduced use of proton pump inhibitors (PPIs) and alleviated symptoms in most patients, and no major complications were encountered.[3,12] A preliminary report has indicated continued benefit of the procedure through 24 months of follow-up.[13]

Thus far unknown is the extent to which the observed benefits may reflect a placebo response. In a meta-analysis of 22 drug trials in patients with erosive/ulcerative

Abbreviations used in this paper: CI, confidence interval; GERD, gastroesophageal reflux disease; HRQL, health-related quality of life; PPI, proton pump inhibitor; SF-36, 36-item Short-Form Health Survey.

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esophagitis, 12% of patients receiving placebo had complete disappearance of symptoms compared with 32% of active drug recipients.[14] The proportion of heartburn-free days in the placebo group was 36%–46% as contrasted with 63%–66% of patients receiving 40 mg esomeprazole in 2 randomized, double-blind, multicenter trials.[15] In a sham-controlled trial of endoluminal radiofrequency energy treatment for GERD, 33% of the sham-treated patients were free of heartburn symptoms versus 61% of the active radiofrequency energy treatment group.[16] There is also the possibility that benefit may be overestimated in noncontrolled trials. The results of a randomized trial comparing Enteryx implantation with a sham procedure are described in this report.

Patients and Methods

Study Design

This multicenter, parallel-group, patient-blinded, randomized, controlled trial was conducted at 4 centers, 2 in Germany and one each in Belgium and Italy, under ethics committee approval from each center (Figure 1). Patients who had rendered their written informed consent were randomly allocated to Enteryx implantation or a sham procedure by means of a set of individually sealed opaque envelopes prepared at a centralized location. Randomized group assignments were generated by computer with a target ratio of 1:1. Patients were not apprised of their group assignments. They were informed that a second treatment would be offered after the 3-month follow-up visit if their symptoms continued. Patient recruitment commenced in November 2001, and follow-up data were collected through August 2004.

End Points

The primary study end point was ≥50% reduction in PPI use compared with baseline. Secondary end points included ≥50% improvement in GERD health-related quality of life (HRQL) heartburn score[17] and the proportion of patients not undergoing a subsequent Enteryx procedure. Trial sample size was selected to attain 80% power in demonstrating a difference in response rate with respect to the primary end point based on the assumption of a 65% response rate in the Enteryx group and a 15% rate in the sham group.

Eligibility

Nonpregnant patients 18 years of age or older with a history of heartburn, regurgitation, or both and American Society of Anesthesiologists Physical Status Classification I or II were eligible. Patients must also have demonstrated a satisfactory symptomatic response (GERD-HRQL heartburn score ≤11) to a previous course of PPI therapy ≥3 months. On PPI withdrawal for a minimum of 10 days, candidates must have experienced symptomatic relapse (GERD-HRQL heartburn score ≥20) and exhibited excessive lower esophageal acid exposure during prolonged pH-metry >12 hours (pH ≤ 4 for ≥5% of total or ≥3% of supine time). Exclusion criteria included the following: non-GERD esophageal motility disorders; diabetic gastroparesis; significant multisystem disease; prior gastric, esophageal, or GERD surgery; scleroderma, dermatomyositis, calcinosis-Raynaud's-esophagus-sclerodactyly syndrome, Sjögren's syndrome, or Sharp's syndrome; persistent esophagitis greater than or equal to grade III (Savary–Miller); Barrett's epithelium; hiatus hernia ≥5 cm; body mass index ≥35 kg/m^2; autoimmune disorder requiring therapy in the preceding 2 years; suspected or confirmed esophageal or gastric cancer; esophageal or gastric varices; and anticoagulant use other than 300 mg aspirin or equivalent per day.

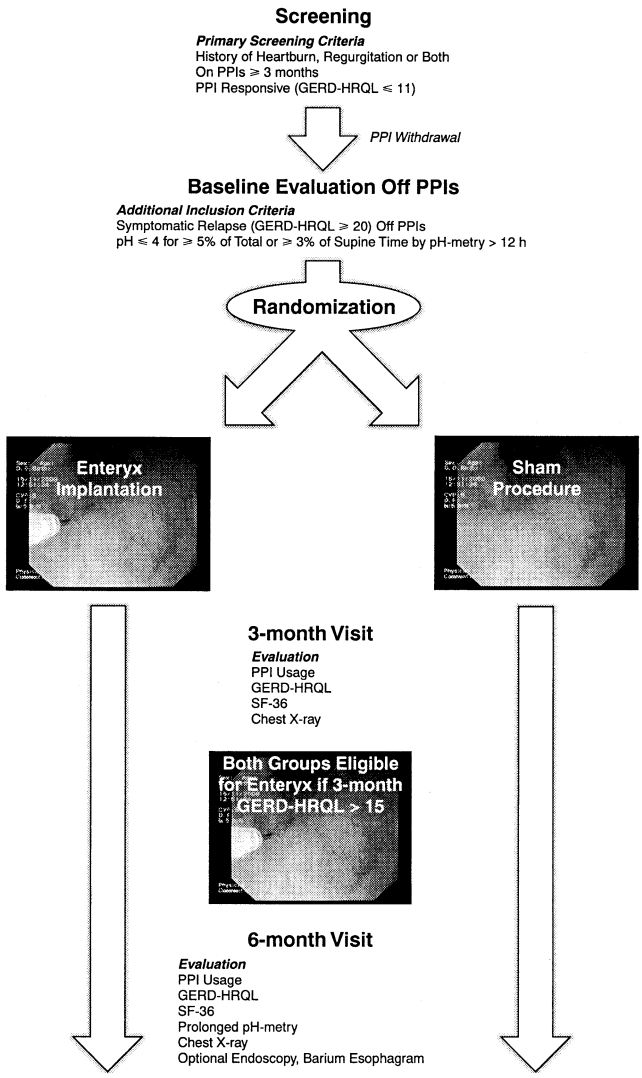

Figure 1. Trial design.

Data Collection

Patient history was elicited at the screening visit, after which patients maintained a diary throughout the trial documenting their use of PPIs. GERD-HRQL and 36-item Short-Form Health Survey (SF-36)[18] questionnaires were completed at all visits (Figure 1). In order to exclude patients with motility disorders, dual manometry/pH-metry was performed at the baseline evaluation while patients were off PPI therapy.