Two-year results of intermittent electrical stimulation of the lower esophageal sphincter treatment of gastroesophageal reflux disease

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Background. *Lower esophageal sphincter (LES) electrical stimulation therapy (EST) has been shown to improve outcome in gastroesophageal reflux disease (GERD) patients at 1 year. The aim of this open-label extension trial (NCT01578642) was to study the 2-year safety and efficacy of LES-EST in GERD patients.*
Methods. *GERD patients responsive partially to proton pump inhibitors (PPI) with off-PPI GERD health-related quality of life (HRQL) of ≥20, 24-hour esophageal pH ≤4.0 for >5% of the time, hiatal hernia ≤3 cm, and esophagitis LA grade C or lower participated in this trial. Bipolar stitch electrodes and a pulse generator (EndoStim BV, The Hague, The Netherlands) were implanted laparoscopically. LES-EST at 20 Hz, 215 μs, 3-8 mAmp was delivered over 30-minute sessions, 6-12 sessions per day, starting on day 1 after implantation. Patients were evaluated using GERD-HRQL, symptom diaries, Short Form-12, and esophageal pH testing at regular intervals. Stimulation sessions were optimized based on residual symptoms and esophageal pH at follow-up.*
Results. *Twenty-five patients (mean age [SD] = 52 [12] years; 14 men) were implanted successfully; 23 patients participated in the 2-year extension trial, and 21 completed their 2-year evaluation. At 2 years, there was improvement in their median GERD-HRQL on LES-EST compared with both their on-PPI (9 vs 0;* $P = .001$*) and off-PPI (23.5 vs 0;* $P < .001$*) baseline scores. Median 24-hour distal esophageal acid exposure improved from 10% at baseline to 4% (per-protocol analysis;* $P < .001$*) at 2 years with 71% demonstrating either normalization or a ≥50% decrease in their distal esophageal acid exposure. All except 5 patients (16/21) reported complete cessation of PPI use; only 2 patients were using a PPI regularly (≥50% of days). There was significant improvement in sleep quality and daily symptoms of heartburn and regurgitation on LES-EST. At baseline, 92% of the subjects (22/24) reported that they were "unsatisfied" with their condition off-PPI and 71% (17/24) on-PPI compared with 0% (0/21) "unsatisfied" at the 24-month visits on LES-EST. There were no device- or therapy-related serious adverse events and no untoward sensation or dysphagia reported with LES-EST.*
Conclusion. *LES-EST is safe and effective for treating patients with GERD over a period of 2 years. LES-EST resulted in a significant and sustained improvement in GERD symptoms, and esophageal acid exposure and eliminated PPI use in majority of patients (16 of 21). Further, LES-EST was not associated with any gastrointestinal side effects or adverse events. (Surgery 2015;157:556-67.)*

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Gastroesophageal reflux disease (GERD) is a global public health problem. The definition of GERD by the Montreal consensus emphasizes both subjective complaints and complications of GERD, defining GERD as "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[1] GERD symptoms are common and affect 10–20% of adults in Western countries and ≤40% in the United States.[2,3] Proton pump inhibitors (PPI) are potent suppressors of gastric acid secretion and have improved the treatment of erosive GERD; however, a substantial number of patients remain symptomatic despite maximal dose therapy. A meta-analysis of randomized, controlled trials indicate a high prevalence of incomplete response or nonresponse of reflux symptoms to PPI therapy.[4,5] A number of mechanisms are thought to contribute to incomplete response, an important one being the continuous reflux of weakly acidic or nonacidic gastric contents while on PPIs, because PPIs target acid secretion, rather than the lower esophageal sphincter (LES) dysfunction permitting persistent and unrestrained reflux of gastric contents into the esophagus.[6]

Inadequate symptom control has been cited as one of the main reasons that drive patients and physicians to seek surgical therapies for GERD.[7] The cost of life-long pharmacologic therapy and potential risks of long-term acid suppression are also of concern to patients and physicians.[8] Surgical fundoplication is effective, but is associated with long-term failures and adverse effects[7,9] This unmet need has led to multiple attempts at developing less-invasive endoscopic and surgical therapies for the treatment of GERD.[10,11]

"A desirable surgical/endoscopic GERD treatment should render an effect that is effective, yet less disruptive, has fewer adverse effects than that of a fundoplication, and be truly reversible."[12] Electrical stimulation therapy (EST) has been used successfully in treating some gastrointestinal motility disorders, such as gastroparesis and fecal incontinence, and has the required characteristics for being that "desirable" surgical therapy for GERD sufferers that are not satisfied with their medical therapy and are not interested in traditional antireflux surgery. The EndoStim LES stimulation system (EndoStim BV, The Hague, The Netherlands) is an implantable neurostimulator developed for the treatment of GERD. We demonstrated previously that temporary LES stimulation resulted in sustained improvement in LES pressure in GERD patients without any effect on LES relaxation.[13] We reported subsequently the safety and efficacy of LES-EST using a permanent LES stimulator implant in GERD patients at their 1-year follow-up.[14] This is the 2-year report of that cohort of subjects treated with LES-EST.

METHODS

Study objectives. The objectives of this prospective, open-label, single-center, treatment-only trial were to assess the safety of chronic intermittent LES-EST and to evaluate the effect of stimulation on GERD symptoms, medication use, esophageal acid exposure, and esophageal motor function in subjects with GERD. The study was registered (NCT01578642) and approved by the local Ethics Committee *Servicio de Salud Metropolitano Oriente Comitè Ètica Cientifico*, Santiago, Chile. All subjects signed an informed consent form before participating in the study.

Subject population. Key inclusion criteria included subjects 21–65 years of age with a history of heartburn, regurgitation, or both for ≥6 months prompting physician recommending continual daily use of PPI before study entry. All had a baseline GERD health-related quality of life (HRQL) score of ≥20 off PPI and a symptomatic response to a course of GERD therapy (≥2 weeks) with a GERD-HRQL score improvement (see below) of ≥10 on PPI. Included subjects exhibited excessive distal esophageal acid exposure during 24-hour pH measurement defined as a pH of ≤4 for >5% of total or >3% of supine, time off, antisecretory therapy. Subjects had a resting LES end-expiratory pressure of ≥5 mmHg on high-resolution manometry. Subjects had esophageal body contraction amplitude of ≥30 mmHg for ≥70% of swallows and ≥50% peristaltic contractions on high resolution manometry. Subjects with esophagitis grade C or lower (LA classification) on upper endoscopy performed within 6 months of enrollment were included. Subjects with Barrett's epithelium (maximal extent (M2) > 2 cm; circumferential extent (C1) > 1 cm), any grade of dysplasia, or a hiatal hernia ≥3 cm were excluded. Subjects with a body mass index of >35 kg/m^2, uncontrolled type 2 diabetes mellitus (defined as a hemoglobin A1c of >9.5 in the previous 6 months), a history of type 2 diabetes mellitus for >10 years, or those with type 1 diabetes mellitus were excluded also. Detailed inclusion criteria, exclusion criteria, and study details have been reported previously.[14]

LES stimulation system: Investigational device description. The LES stimulation system is made up of 3 components: a bipolar electrical stimulation lead, an implantable pulse generator (IPG), and an external programmer (Fig 1, *A*).

Stimulation lead. A sterile, bipolar stitch electrode stimulation lead is used in conjunction with