

Reviewed by 00253974

Regarding the thesis provided by this article we examined the recent data published in different journals, a.e. the study group published similar data in the beginning of this year. We can't determine significant new aspects or results. Furthermore, the examined group size, especially in the PPI-responding group is really low.

Response

While the previous publications indeed provided results of EST of the whole cohort of implanted patients, we believe the distinction made in this paper between partial responders and complete responders is clinically relevant. GERD patients opt for alternative therapy to PPI for a variety of reasons that however fall into 2 main categories: those who do not respond adequately to PPI, and those who respond, but do not want to take PPI on a chronic basis. One would expect the latter group to do better on LES-EST as compared to the incomplete responder group (after all, a good predictor of response to Nissen fundoplication is response to PPI therapy and vice versa). Hence, the demonstration that partial responders do as well on EST as complete responders is clinically important.

Reviewed by 00068404

Thank you, I trust that you did a great job to do this clinical study. As a medical doctor, it seems we can do nothing to the refractory GERD. I think LES-EST will be another choice for us. About half a year ago, I read the paper "Long-term results of electrical stimulation of the lower esophageal sphincter for treatment of proximal GERD". I think this study was new and interesting. I still have 2 questions: 1. would you please tell us when this study started? Compared with the previous study, some patients joined both two studies? We started enrolling patients in the single center study, conducted in Santiago, Chile in 2010. The papers published thus far document the sustained response to therapy over time, of the whole cohort of patients (up to 3 years). In this paper we document the response of 2 subgroups within the cohort, responders vs. incomplete responders.

2. I trust the stimulation parameter is important to the GI electrical stimulation, especially for the pulse width. Why do you choose the 215µsec? The acute human study (Rodríguez L et al. Short-term electrical stimulation of the lower esophageal sphincter increases sphincter pressure in patients with gastroesophageal reflux disease. *Neurogastroenterol Motil.* 2012; 24: 446-50) showed that both high energy stimulation (low frequency/long pulse duration) and low energy stimulation (high frequency / short pulse duration) were equally effective in enhancing LES tone. Given the energy efficiency of high frequency stimulation, and conservation of battery life, we opted for these pulse parameters

Reviewed by 00039422

This paper is concerning an interesting topic, i.e. alternative treatment to PPI for patients poorly responding to PPI. Obviously, as pointed by the authors, the paper has two limits: the very low number of patients in both arms (one arm include 7 patients), which strongly reduces its power, and the “open label” design. Likely more data should be elaborated in order to support the final conclusions.

Generally speaking, EST cannot be considered a theoretical alternative to surgery. While surgical therapy is generally not recommended in patients who are complete non-responders to PPI therapy, as stated in the Discussion, nevertheless the barrier created by a fundoplication is valuable even for weakly acidic or non acidic reflux, hence being theoretically more effective than medical treatment. The same observations could be applied to EST, without a particular difference with traditional antireflux surgery. Accordingly, in the discussion I would not emphasize the limits of antireflux surgery in contraposition to EST: indeed, EST might be more an alternative to medical than to surgical treatment. The significant reduction in acid reflux by EST (an intervention that does not affect gastric acid secretion) strongly suggests that a similar reduction would have been observed in weakly acidic reflux, had it been assessed. Hence the technique is more in line with a surgical anti reflux than a medical treatment that reduces only the acidic content of the refluxate. The discussion does not dispute the therapeutic merit of Nissen fundoplication; rather, the emphasis is on the adverse effects of the procedure. After all, the reason for the continuous search for an alternative intervention is not so much the desire for a more effective one, but rather, for one with less adverse effects.

EST was considered by the authors as an effective treatment also for non-acidic reflux. Consequently, its efficacy would be much more supported by a pH Impedance test than by a simple measurement of esophageal acid exposure. The barrier consequent to the EST would be confirmed more strongly. At least this issue should be mentioned in the Discussion. Actually, it would be of the utmost interest to evaluate the system in patients with a positive impedance for reflux and absent or weak acid reflux. We agree with the reviewer that the use of pH impedance would have provided valuable data on weakly acidic reflux. However, since EST is not expected to affect gastric acid production, it is anticipated that a reduction in acidic reflux episodes should be accompanied by a similar reduction in weakly acidic episodes (unlike the case with PPI, where the reduction in acidic reflux events is accompanied by a detection of a larger number of weakly acidic ones).

A further limit of the technique is the presence of a hiatal hernia larger more than 3 cm, a finding which is not rare in patients with esophageal reflux, therefore limiting the indications of the procedure. Future studies might stimulate to consider EST also for patients with hiatal hernia, but the issue should be discussed more in detail. We agree with the reviewer point. Large hiatal hernia is usually excluded in initial trials of antireflux measures (endoscopic or surgical). Future experience may provide more information regarding the role of EST in patients with large hiatal hernia. The point is raised in the discussion section, under limitations of the study

Esophageal acid exposure was evaluated during 24-hour pH-measurement and defined as pH < 4 for > 5% of total or > 3% of supine time. I would add De Meester score, as it was reported in the paper published by the same authors in Surgery in 2015 and included in the References. Added

Although the technique has already been reported elsewhere by the authors (Surgery 2015; 157: 556-567), a more detailed description would be welcomed even in this paper, especially considering the presence of the related figures in the manuscript. The description of implantation technique was expanded.

The authors state that electrical stimulation can be optimized using the external programmer to tailor therapy to individual patients' needs. Is there any variation or any difference between the groups of responders and not responders to PPI? There has been any adjustment during time in the same patient? It would be nice to have the data of stimulation characteristics, especially in the long term follow-up. There was no major difference in adjustments between the 2 groups; both received the same number of sessions, voltage in the complete responder group was 1.9 (2.3-3, median and range), while in the incomplete responder group it was 1.2 (2.56-3.5, median and range). Polarity was switched in 3/7 in the complete responder group and in 5/14 in the incomplete responder group. Short clarification added to manuscript

One patient quit the study for an elective Roux-en-Y gastric bypass surgery for uncontrolled Type 2 diabetes. Was the diabetes controlled when the patient was enrolled? Per enrollment criteria HbA1c has to be less than 9.5 to be included in the study. When enrolled the site checked all exclusion criteria and indicated that HbA1c is minimally above normal.

At page 16, line 9 from below: eliminate "at" which is repeated twice. corrected

At page 17, lone 4 from above: "are" is needed before the word "completely" corrected

Although 100% of responders to PPI were satisfied with their condition at one year, 30% of them are still taking PPI in spite of the EST; hence satisfaction could be consequent to medical treatment instead of EST efficacy. Moreover, the not responder group has overall better results than responder. Both issues need to be discussed. All patients were on PPI before implant, hence satisfaction after implant cannot simply be attributed to PPI use. Significant reduction in regurgitation, that is not achieved with PPI could be one of the reasons.

Apparently, at 24 months the outcome is less successful than at one year. Evaluation of long term results is obviously needed and this should be emphasized in the Discussion. We agree with the reviewer comments

At page 18, 2nd line from below: the first word should be "and" instead of "And". corrected

At page 20, first paragraph, the authors discuss about regurgitation, which is recognized as a true indication to antireflux surgery. However, according to the evaluation performed in the patients enrolled in this study, regurgitation was not clearly assessed (pH impedance evaluation could give more precise results). Effect of EST on frequency and severity of regurgitation, both during the day and at nighttime at baseline vs, EST is presented in figure 2B and Table 1.

At the same page, line 6 from above, “Karallas” should be substituted by “Kahrilas”.corrected

English language may be improved.