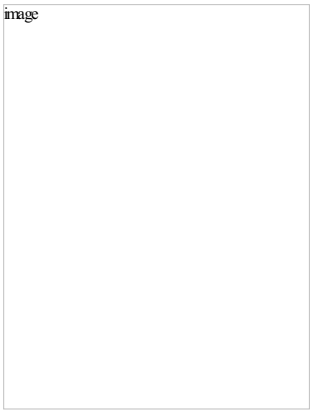

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Electrical Stimulation of the Lower Esophageal Sphincter to Address Gastroesophageal Reflux Disease after Sleeve Gastrectomy

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Short title: Electrical Stimulation of LES for post-LSG GERD

Background:

Laparoscopic Sleeve Gastrectomy (LSG) can result in de novo and worsen preexisting Gastroesophageal Reflux Disease (GERD). Post-LSG patients with GERD refractory to Proton Pump Inhibitors (PPI) usually undergo more invasive, anatomy-altering gastric bypass surgery (RYGB). Lower Esophageal Sphincter (LES) electrical stimulation (ES) preserves the anatomy and has been shown to improve outcomes in GERD patients.

Objective:

To evaluate the safety and efficacy of LES-ES in post-LSG patients with GERD not controlled with maximal PPI therapy.

Setting:

Prospective, international, multi-center registry

Methods:

Patients with LSG-associated GERD partially responsive to PPI underwent LES-ES. GERD outcomes pre- and post-stimulation were evaluated based on Quality of Life (GERD-HRQL), esophageal acid exposure (after 6-12 months) and PPI use.

Results:

17 patients (11 female, 65%), treated at 6 centers between 05/14 - 10/16 with a median follow-up of 12 months (min 6-max 24), received LES-ES. Median age was 48.6y (IQR 40.5–56), median Body Mass Index 31.7 kg/m2 (27.9–39.3).

All patients were on at least daily PPI preoperatively; at last follow-up, 7 (41%) were completely off-PPI, 5 (29%) took PPI on an intermittent basis and 5 (29%) were on single-dose PPI. Median GERD-HRQL scores improved from 34 (on-PPI, 25-41) at baseline to 9 (6-13) at last follow-up (off-PPI, $p<0.001$). Percentage of time with esophageal pH<4 improved from 13.2%(3.7–30.7) to 5.8%(1.1–54.4), $p=0.01$.

Conclusion:

LES-ES in post-LSG patients suffering from symptomatic, PPI-refractory GERD resulted in significant improvement of GERD-symptoms, esophageal acid exposure and need for PPI. Preserving the post-LSG anatomy, it offers a valid option for patients unable or unwilling to undergo RYGB.

Keywords:

Electric Stimulation Therapy; Lower Esophageal Sphincter; Gastroesophageal Reflux; Proton Pump Inhibitors; Quality of Life; sleeve gastrectomy; Bariatric surgery; esophageal pH; postgastrectomy syndromes; Prospective studies

Introduction:

Morbid obesity is recognized as a major public health issue that contributes to serious health risks. Bariatric surgery has been demonstrated to be the most efficacious method to achieve sustainable weight loss and resolution of comorbidities among the morbidly obese(1, 2).

In recent years, laparoscopic sleeve gastrectomy (LSG) has become the most frequently preformed bariatric procedure, in both, a stand-alone or a prelude to staged duodenal switch (1, 3). Contributing factors to its widespread acceptance are technical simplicity, low morbidity and results comparable to Roux-Y Gastric Bypass (RYGB), for weight loss and control of metabolic syndrome(2). Preservation of anatomy predisposes this procedure for patients in need for access to the biliary tree, stomach and duodenum. Further, complications associated with RYGB such as dumping syndrome, small bowel obstruction due to internal hernia and nutrient deficiencies are avoided.

The prevalence of Gastroesophageal Reflux Disease (GERD) in bariatric patients is increased; up to 70% of patients have symptomatic GERD and half of patients undergoing bariatric surgery have erosive esophagitis in the preoperative evaluation(4, 5). In contrast to RYGB, there are reports of SG worsening pre-existing GERD or causing new-onset GERD(6-9). So far, GERD after LSG, not sufficiently controlled by medication, is addressed by conversion to RYGB(10). Yet, as every revisional procedure, this carries an increased morbidity but particularly abrogates the initial intention of LSG as anatomy-preserving procedure(10, 11).

Electrical stimulation of the Lower Esophageal Sphincter (LES) is a novel surgical option that has been shown to normalize LES pressure and esophageal acid exposure in GERD patients without altering the anatomy(12-15). The aim of this study was to evaluate the safety and efficacy of electrical LES stimulation in LSG patients with refractory GERD despite maximum dose PPI therapy.

Methods:

Data collection:

Anonymized data of post-LSG patients with a follow-up of >6 months and GERD treated with LES stimulation therapy (EndoStim®, BV, Nijmegen, Netherlands; currently filing for FDA approval) were extracted from a prospective, web-based, international multi-center registry, tracking symptomatic and objective outcome, registered at the clinical trials registry of the National Institutes of Health (NCT 02441400). Patient symptoms, medication use and esophageal tests pre- and post-LES stimulation therapy were analyzed.

Surgical technique and LES stimulation:

Two electrodes were sewn into the esophageal wall laparoscopically 1cm apart in the LES region (Fig 1), the lead body was exteriorized through one of the laparoscopic ports and the pulse generator was implanted in a subcutaneous pocket in the left upper abdomen. Small hiatal hernias (<2cm) were addressed with hiatoplasty (posterior or combined anterior and posterior) hiatoplasty at the surgeons' discretion. Preoperative bigger hiatal hernias were a contraindication. LES stimulation was initiated during the implant procedure, PPI therapy was discontinued 3-4 weeks later. Patients with

residual or recurrent symptoms despite optimization of their stimulation parameters were treated with rescue GERD medications.

The standardized stimulation pulse (215μs wide and nominally 5mA in amplitude) is monophasic followed by a charge-balancing phase. The stimulation pulse is delivered at a rate of 20Hz and continues for a period of 30 minutes. Up to twelve 30-minute sessions are delivered per day. Electrical stimulation can wirelessly be optimized to tailor the delivery to individual needs by adjusting amplitude and electrode polarity to address suboptimal symptom or pH response beginning 6 months after the procedure.

Symptom assessment and pH-monitoring:

GERD symptoms were assessed using the validated GERD–HRQL- questionnaire which provides a composite score of maximum 50 points(16). Assessment was carried out at baseline (prior to implantation) with the patient on PPI therapy and at every follow-up (every 6 months in the first 2 years, then yearly). Esophageal acid exposure was assessed at baseline and after 6-12 months of LES stimulation therapy using 24-hour esophageal pH-metry. Sensors were positioned in the esophageal body 5cm above the manometric upper border of the LES with the patient off PPI therapy for at least 5 days. Further, use of PPI medication and anthropometric parameters were recorded at each follow-up visit.

Descriptive statistics were used for demographic variables. Data were compared using two-tailed Student's t-test, Friedman test or Wilcoxon signed-rank test. A two- sided p-value of <0.05 was considered significant. Data were reported as medians with interquartile range (IQR) unless otherwise stated.

Results:

17 patients (11 female, 65%), treated at 6 centers between 05/14 - 10/16 with a median follow-up of 12 months (min 6- max 24), were included. No patient was lost to follow-up. Median age was 48.6y (IQR 40.5 – 56), median BMI at time of implantation was 31.7 kg/m2 (27.9 – 39.3), there was no significant decrease during the follow-up (after 6 months 28.5kg/m2 (23.9 – 34.8), after 12 months 29.8kg/m2 (23.6 – 35), p=0.2).

There were no serious adverse events related to the device or procedure, and there were no reoperations or device removals within the follow-up.

Preoperatively, all patients were using daily double- or higher dose PPI (single dose defined as 40mg pantoprazole or equivalent). At their last follow-up, 5 patients (29%) were on single dose-, 7 (41%) completely off-PPI and 5 (29%) took PPI on an intermittent basis.

All patients reported improvement in their GERD symptoms after initiation of LES stimulation. Median GERD-HRQL scores (Fig 2a and 2b) at baseline (on-PPI) were 34 (25-41) which improved to 9 (6-13) at last follow-up (off-PPI, p<0.001).

Evolution of median esophageal acid exposure is depicted in Figure 3. Percentage of time with pH<4 improved from 13.2% (3.7 – 30.7) to 5.8% (1.1 – 54.4), p=0.01; normalization (< 4% of esophageal pH < 4) was observed in 7 (41%) and worsening in

2 patients (12%). Yet, in both patients, GERD-HRQL improved and both were responsive to PPI therapy.

Discussion:

This study reports the outcome of post-LSG patients with refractory GERD addressed with electrical stimulation of the LES over a median follow-up of a year (range 6-14 months). This treatment led to a significant improvement of both GERD symptoms, esophageal acid exposure and reduction in GERD medication use.

Morbid obesity is associated with GERD and esophageal motility disorders, the prevalence is estimated up to 70%(4, 5, 17-19). There is a linear relationship not only between BMI and GERD, but rather between central obesity and GERD(20). Yet, central obesity complicates bariatric procedures and is one of the main reasons - together with the resulting comorbidities – for the popularity of LSG(21). Morbid obesity increases the intraabdominal pressure having an effect on intragastric pressure and the gastroesophageal pressure gradient, and leads further to a higher rate of hiatal hernias and postprandial transient LES relaxations (TLESR)(22). Further, LES pressures are lowered, and there is high incidence of ineffective esophageal motility(23, 24).

The effects of LSG on GERD are controversially discussed, yet the vast majority of studies report a worsening of pre-existing and a substantial rate of de-novo GERD(8, 25-27).

Depending on duration of follow-up, measures to detect GERD and operative technique, the incidence of de novo post-LSG GERD ranges up to 47% in symptoms and 63.5% endoscopically(7, 8, 19, 26). Further troubling is a high rate of asymptomatic GERD in bariatric patients of so far unknown importance and an association of worse outcome after LSG with GERD regarding weight loss and resolution of comorbidities(8, 28, 29). Post-LSG Barrett's esophagus has a high incidence and occurs unrelated to symptoms(30). In addition, with rising numbers of LSG, this problem might aggravate in the near future as most studies so far describe a selected patient group with less GERD; so far, most patients with pre-existing higher-grade GERD are denied the benefits of LSG and proposed RYGB instead(31).

A multitude of factors have an influence on post-LSG GERD after LSG(27). Technical factors such as proximity of the staple to the LES have an impact on its function, disruption of sling fibers lead to a decrease of LES pressure and shortening of LES, as showed by manometric pre- and postoperative evaluation(5, 24). LSG results in decreased gastric compliance provoking a possible increase of TLESR(22). Further, another study showed a high rate of ineffective esophageal peristalsis after LSG(23).

Electrical Stimulation of the LES leads to a sustained reduction of GERD symptoms and improvement of esophageal acid exposure in the majority of patients(12-14). It is a procedure with minimal morbidity, also in the small group reported here. The underlying mechanisms have yet to be elucidated in detail; it has a positive impact on LES pressure and LES length and may improve esophageal motility and reduce the frequency of TLESR(15). In the context of post-LSG GERD, it offers the distinctive advantage of preserving the anatomy. This study shows it to be safe and technically

feasible. It offers a significant improvement of esophageal acid exposure with a normalization in almost half of patients. A longer follow-up might lead to an even higher rate, as the maximum effect has to be expected after 9 months, yet the median objective follow-up in this study was 6 months. Symptomatic control, in terms of PPI use and standardized questionnaires, was excellent, and comparable to RYGB. Even more, the patient population included was non-responsive to PPI and had a rather high esophageal acid exposure.

There are limitations to this study. It is an open-label, multicenter design with a small sample size including a heterogeneous patient population from a self-reported patient registry. Postbariatric patients are different than other GERD patients with different comorbidity profiles and probable different reasons for GERD. These data are preliminary; a larger sample size with a longer follow-up in a prospective, randomized, double-blind, sham-controlled design is needed to validate these results.

Conclusions:

Electrical stimulation of LES in post-LSG patients suffering from symptomatic GERD refractory to medication led to a significant improvement of GERD-symptoms, esophageal acid exposure and overall decrease of need for PPI. Preserving the post-LSG anatomy, it offers a valid option for patients unable or unwilling to undergo RYGB.

Disclosures:

Y.B. received travel reimbursements from Endostim, all other authors declare that they have **no conflict of interest.**

Tables and Figures:

Figure 1: Electrodes sewn into the esophageal wall beneath the Lower Esophageal Sphincter

Figure 2a: Evolution of symptoms, assessed with the GERD-HRQL score (max 50), shows a significant and sustained improvement over time. Depicted in both figures are medians (box) with interquartile ranges (error bars).

Figure 2b: Improvement of symptoms from preoperative baseline (left column) to last follow-up (right column), according to postoperative proton pump inhibitor use.

Figure 3: Evolution of esophageal acid exposure, in percentage of time with esophageal pH <4 (dotted line at 4%). Overall significant improvement, median follow-up was 6 months.

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