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ORIGINAL ARTICLE

Closed-loop gastric electrical stimulation versus laparoscopic adjustable gastric band for the treatment of obesity: a randomized 12-month multicenter study

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OBJECTIVE: To compare the weight loss, change in quality of life (QOL) and safety of closed-loop gastric electrical stimulation (CLGES) versus adjustable gastric band (LAGB) in the treatment of obesity.

METHODS: This multicenter, randomized, non-inferiority trial randomly assigned the patients in a 2:1 ratio to laparoscopic CLGES versus LAGB and followed them for 1 year. We enrolled 210 patients, of whom 50 were withdrawn preoperatively. Among 160 remaining patients (mean age = 39 ± 11 years; 75% women; mean body mass index = 43 ± 6 kg m^{-2}) 106 received CLGES and 54 received LAGB. The first primary end point was non-inferiority of CLGES versus LAGB, ascertained by the proportion of patients who, at 1 year, fulfilled: (a) a ⩾20% excess weight loss (EWL); (b) no major device- or procedure-related adverse event (AE); and (c) no major, adverse change in QOL. Furthermore, ⩾50% of patients had to reach ⩾25% EWL. The incidence and seriousness of all AE were analyzed and compared using Mann–Whitney's *U*-test.

RESULTS: At 1 year, the proportions of patients who reached all components of the primary study end point were 66.7 and 73.0% for the LAGB and CLGES group, respectively, with a difference of –6.3% and an upper 95% CI of 7.2%, less than the predetermined 10% margin for confirming the non-inferiority of CLGES. The second primary end point was also met, as 61.3% of patients in the CLGES group reached ⩾25% EWL (lower 95% CI = 52.0%; $P < 0.01$). QOL improved significantly and similarly in both groups. AE were significantly fewer and less severe in the CLGES than in the LAGB group ($P < 0.001$).

CONCLUSIONS AND RELEVANCE: This randomized study confirmed the non-inferiority of CLGES compared with LAGB based on the predetermined composite end point. CLGES was associated with significantly fewer major AE.

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INTRODUCTION

The prevalence of morbid obesity among adults and children in developed countries of the Western hemisphere has steadily increased in the past few decades,[1] representing a heavy and costly public health burden.[2–4] In these countries, it is estimated that over one quarter of the general population will be obese by year 2030,[3] whereas the US National Health and Nutrition Examination Survey from 2007–2008 reported that the body mass index (BMI) of approximately one-third of adults was ⩾30 kg m^{-2}.[5] The long-term medical management of morbid obesity is notoriously challenging and frustrating, from both the patients' and the caregivers' vantage points. Besides lifestyle modifications and a few drugs of limited long-term efficacy and associated with high rates of adverse effects, bariatric surgery has been the main, most successful therapeutic alternative for over a decade.[6] Among the laparoscopic procedures most frequently performed, gastric bypass and the sleeve gastrectomy have been most effective and the adjustable gastric band (LAGB) has been has been associated with the lowest rate of early postoperative complications. Though the laparoscopic approach has increased the safety of these operations, all but LAGB cause permanent changes to the gastrointestinal tract, and all are associated with major peri- and postoperative complications.[7,8] Consequently, bariatric surgery is ultimately offered to a small proportion of obese patients.[9]

Gastric electrical stimulation (GES) to treat obesity was introduced in animal experiments nearly 20 years ago.[10] The mechanism of action depends on the targeted gastric region or nerve, but includes: impairing the physiological slow waves of gastric electrical activity, and inducing gastric distension and inhibits peristalsis, leading to delayed gastric emptying and increased satiety.[11] Furthermore, the promotion of weight loss by stimulation of the vagus nerve was discovered serendipitously during treatment of epilepsy,[12] and another proposed mechanism of action for GES involves neuromodulation of the vagus. Multiple experimental and clinical studies have confirmed the relative safety and efficacy of GES in the management of obesity.[13] In recent years, a closed-loop (CL), meal-triggered GES was developed, which, in observational studies, has been safe, well-tolerated and effective up to 12 months of follow-up.[14,15] However, this putatively superior CL system has not been compared with other treatments of obesity.

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This multicenter, randomized study was performed to test the hypothesis that closed-loop gastric electrical stimulation (CLGES) is not inferior to LAGB therapy based on a composite end point that includes weight loss, quality of life (QOL), and safety, in the treatment of obese or morbidly obese patients.

STUDY POPULATION AND METHODS

This study was reviewed and approved by the review boards of all participating institutions, and all patients were required to sign an informed consent at study enrollment. Patients were prescreened using the Three-Factor Eating questionnaire (TFEQ).[16] The three dimensions of eating behavior probed by TFEQ are cognitive restraint, disinhibition and feelings of hunger, including sweets craving and emotional eating. It has been used to predict the success of lifestyle and pharmacological treatments,[16,17] and before and after restrictive procedures, such as vertical banded gastroplasty and adjustable gastric banding.[18] After completing the TFEQ, patients were medically screened for entry into the study. They were eligible if (a) they were between the ages of 18 and 60 years, (b) their BMI was between 45 and 55 kg m^{-2} or between 35 and 45 kg m^{-2} with an obesity-related disorder, (c) the H1 Ab was $\leqslant 7.0$ in absence of insulin therapy and (d) they had no history of bariatric surgery. (A full list of screening criteria is available in supplementary material Supplementary Table 1). Those eligible for the study were enrolled by the site investigator. Participants were then assigned in a 2:1 ratio to CLGES versus LAGB, using a randomization table, which was implemented electronically by an independent clinical research organization (MedPace, Inc), providing concealment of the allocation sequence until the time of assignment. The treatment assignment within each site was balanced with the use of random permuted blocks.

Patients assigned LAGB underwent an endoscopic examination to confirm the integrity of the stomach, whereas the patients assigned to CLGES underwent, and had a symptomatic response to a preoperative, custom-designed endoscopic 'fullness intensity threshold test' (eFITT), performed to determine whether GES similar to that administered by the implantable system, though delivered endoscopically, elicited a prominent response. The eFITT was performed with a temporary lead introduced inside the gastric cavity, fixed to the stomach wall and connected to a system analyzer and electrical stimulator. Patients who experienced nausea, salivation, satiety, bloating, belching, epigastric discomfort or other manifestations attributable to the stimulation, and described as disagreeable to a level 3 on a visual analog scale ranging from 1 to 4, were candidates for implantation of the system. The study was conducted at nine European medical centers (supplementary material Supplementary Table 2) chosen on the basis of the qualifications of the investigators, their ability to recruit patients for the study and the availability of sufficient resources to carry out the study procedures. Because of the low proportions of non-whites living in the four countries participating in this trial, its population consisted nearly exclusively of Caucasians. The study is registered at ClinicalTrials.gov (Identifier: NCT01448785)

Study objective

The main objective of this study was to compare the amount of weight loss, change in QOL and safety of CLGES versus adjustable LAGB, in the treatment of obese or morbidly obese patients.

Study end points

The first primary study end point was to confirm the non-inferiority of CLGES compared with LAGB, ascertained by the proportion of patients who reached all of the following components:

(a) greater or equal to 20% excess weight loss (EWL) between the system implantation and the end of follow-up; (b) no major device- or procedure-related adverse event (AE); and (c) no major, adverse change in QOL, using the Impact of Weight on Quality Of Life-Lite (IWQOL-Lite) questionnaire.[19]

The second primary end point required that a $\geqslant 25\%$ EWL be reached by $\geqslant 50\%$ of the patients.

The secondary efficacy end points of the study, examined at 6 and 12 months of follow-up, were: (a) change in QOL, using the IWQOL-Lite[19] and the Beck Depression Inventory (BDI)-II[20] questionnaires; (b) change in eating behavior, using the TFEQ,[16] and (c) changes in blood pressure, blood lipids and hemoglobin A1c concentrations.

The safety end points of the study were (a) incidence and seriousness of all AE, (b) incidence of device- or procedure-related AE and (c) prevalence of abnormal laboratory results, judged clinically significant by the investigator.

Study procedures

Closed-loop gastric stimulator description and implantation. abiliti (Intrapace Inc. San Jose, CA, USA) consists of a gastric stimulator and lead implanted laparoscopically, a programmer, telemetry wand and a temporary screening lead used to perform the eFITT, as described earlier. The battery-powered stimulator is equipped with telemetry that enables bi-directional communications with a programmer. Telemetry was used to confirm the integrity of the stimulation electrodes, monitor the stimulator's battery and program the electrical therapy. The details of the surgical implant procedure and CLGES operation have been published previously.[14,15] The system detects when the patient eats or drinks and, in response, delivers electrical stimuli targeted to the stomach's lesser curvature in a region richly innervated by vagal neural fibers. The device also records the eating and drinking events detected by a food sensor, and the patient's physical activity, sleep trends and estimation of total daily energy expenditure recorded by a triple axis accelerometer housed inside the stimulator. The medical team can access the recorded data, using a programmer and wand to communicate with the implanted system. In addition, the patients can view their recorded activity data and eating events via an Internet-based interface.

Figure 1a illustrates the implanted system. The distal end of the permanent lead contains the transgastric probe, which houses the food sensor. The probe is inserted into the gastric lumen, whereas a silicon flange remains on the outside and is sutured onto the serosal surface of the stomach.[14] A proximal stimulation electrode was attached with two suture wings to the external surface of the stomach's lesser curvature, near the vagus nerve. A subcutaneous pocket was created in the left upper abdominal quadrant, where the lead was connected to the stimulator and buried immediately over the fascia. At the end of the implant procedure, the device was activated to deliver a pre-programmed, low intensity therapy.

Gastric band implantation. LAP-BAND LAGB (Apollo Endosurgery, Inc, Austin, TX, USA) implanted in 50 patients, or REALIZE LAGB (Ethicon Endo-Surgery, a Johnson & Johnson Company, New Brunswick, NJ, USA) implanted in 4 patients, encircled the proximal part of the stomach, at the gastric cardia to limit the amount of food entering the stomach, and were connected to a subcutaneous port and reservoir (Figure 1b). The LAGB systems were implanted using the pars flaccida technique, according to the procedural standards adopted by the surgeons at each participating medical center. The band, initially deflated, was progressively inflated via the subcutaneous port during subsequent ambulatory visits.

Adverse events

All AE were recorded, regardless of their putative relationship to a device or procedure, though only the device- or procedure-related AE are reported here. The gastrointestinal AE included nausea vomiting, dysphagia, heartburn, epigastric pain, belching and liquid intolerance, and the body as a whole AE consisted of anxiety, hair loss, headache and arthralgia. Other device-related AE included painful stimulation, pulse generator replacement or revision, pocket discomfort or dilatation, lead fracture, twiddler syndrome and band slippage. The rating criteria were similar to those used in LAGB premarket approval studies.[21,22] They were classified as (a) minor when easily tolerated, possibly requiring the prescription of a new pharmaceutical, or nutritional advice, (b) moderate when they interfered with usual activities requiring an unscheduled visit or an adjustment of the stimulation or of the band and (c) major when they required a re-hospitalization for a surgical or endoscopic intervention. AE occurring within 2 weeks of the CLGES or LAGB implantation procedures were classified as perioperative. The site investigator determined the type and severity of each adverse event.

Patient follow-up

At each follow-up visit the CLGES group underwent an iFITT, using the implanted electrode, to test and adjust the devices, and tailor the stimulation to produce the desired sensation of fullness. At the first follow-up visit, using an external programmer, the caregiver tailored the therapy delivery to each patient's eating schedule. During programmable 'allowed' time-periods, (for example, meal times and authorized

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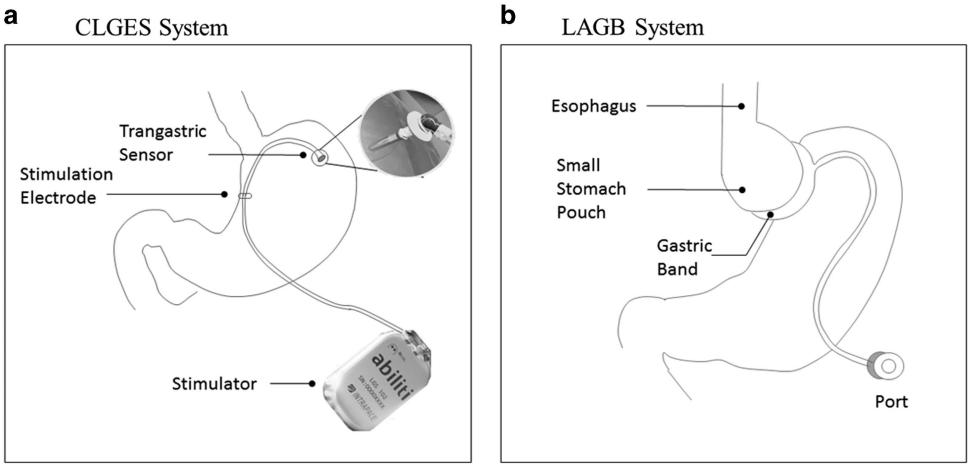

Figure 1. (**a**) The transgastric sensor, implanted in the anterior wall, body-fundus region, detects the entry of food into the stomach, triggering the gastric stimulator implanted subcutaneously in the left upper abdominal quadrant, to deliver electrical therapy via the stimulation electrode. The stimulating electrode is attached to the lesser curvature, at the point where the Nerve of Latarjet is divided into three branches. (**b**) The implanted gastric band system is shown with the gastric band encircling the proximal stomach at the level of the cardia, creating a small gastric pouch. The access port is implanted subcutaneously, in or on the rectus muscle, enabling percutaneous adjustments of the band.

snacks) the therapy produced satiety to limit the food consumption, whereas during 'disallowed' periods (for example, nocturnal eating), more intense stimulation was delivered to cause discomfort and force the discontinuation of consumption. The medical and surgical teams at the study sites were trained in the use of the CLGES system.

The LAGB group underwent adjustments according to the state of the art care to avoid over-tightening of the band. The adjustments were based on weight loss and patient feedback, as is standard practice.[23]

Both study groups received diet and exercise counseling at the time of discharge from the hospital and at each visit, according to standard post-surgical protocols for bariatric patients. In the CLGES group the dietary and exercise counseling was supplemented by the sensor-based records of the patient's eating and activity behavior downloaded from the device.

Patients in both study groups were instructed to keep a 7-day diary of their daily food consumption, which they returned with their list of pharmaceuticals at each follow-up visit, scheduled at 4-week intervals. At 3, 6 and 12 months, they underwent a detailed physical examination and repeat laboratory measurements, and at 6 and 12 months, they completed the follow-up QOL and TFEQ.

All data, collected at each investigative site by dedicated staff designated by the sponsor, were entered in a computer database for later analysis by the site investigators and the sponsor's clinical department. A field clinical engineer assigned to the study sites assisted the investigative staff throughout the study.

Changes in patients with cardiovascular risk factors

The changes observed in patients presenting at baseline with hypertension, diabetes or hyperlipidemia were analyzed for each study group and compared. Hypertension was defined as a systolic blood pressure >139 mmHg or a diastolic pressure >89 mmHg.[24] Diabetes was defined as a fasting HbA1c $\geqslant 6\%$ of total hemoglobin, which includes a pre-diabetes very high risk category as defined by an International Expert Committee Report in 2009.[25] Dyslipidemia was defined as a total cholesterol >200 mg dl^{-1}, a high-density lipoprotein cholesterol <40 mg dl^{-1} in men and <50 mg dl^{-1} in women, a low-density lipoprotein cholesterol >130 mg dl^{-1} or a blood triglyceride concentration >150 mg dl^{-1}.[26]

Statistical analysis

Descriptive statistics for all efficacy and safety end points include the number of observations, means ± s.d. and ranges for continuous variables, crude event rates and rates per patient-year for recurrent events, counts and percentages for categorical variables and two-sided 95% confidence intervals (CI).

Sample size calculations. We hypothesized that CLGES was non-inferior to LAGB for the treatment of obesity. On the basis of previous publications,[21,27] we estimated that 61% of patients in the LAGB and 74% of patients in the CLGES group would reach the composite study end point. On the basis of these estimates, and assuming a 10% inferiority margin, an enrollment of 150 patients, randomly assigned in a 2:1 CLGES: LAGB ratio, was required to confirm the non-inferiority of CLGES with an 80% power. The target enrollment was increased to 165 patients to allow a 10% attrition.

The 'full analysis set' includes all patients who were treated. It was used to analyze all study end points. Missing 12-month measurements of the percentage EWL were imputed using the last observation carried forward method.

Efficacy end points. The non-inferiority of CLGES compared with LAGB was tested and analyzed, using the composite primary end point described earlier, and a one-sided 95% upper CI to show a $>10\%$ between-groups difference, including all treated patients. Furthermore, the proportions of patients who reached a $\geqslant 25\%$ EWL were measured in each study group and compared, using Fisher's exact test.

Safety end point. The incidence of all AE was measured. AE were classified by the investigators as minor, moderate or major, as perioperative or long-term and as device-related or -unrelated. The severity of AE, up to 1 year of follow-up in each study group was compared, using the Mann–Whitney *U*-test, and the incidence of AE was compared using the Fisher's exact test.

A *P*-value <0.05 was considered significant. The SAS statistical package, version 9.3 (SAS Institute Inc., Cary, NC, USA) and Minitab 17.1.0 (Minitab Inc., State College, PA, USA) were used for these analyses.

RESULTS

Over a 14-month enrollment period, 722 patients were pre-screened at 9 medical centers (Supplementary Table 2), using the TFEQ. Three hundred and twenty-four passed the prescreening and were screened using the inclusion/exclusion criteria, from which 114 were found to be not eligible or declined to participate, and 210 were enrolled. Fifty of those enrolled were withdrawn preoperatively for miscellaneous reasons, including 16 patients in the CLGES group, who were withdrawn because of a negative response to the eFITT. Among the remaining patients withdrawn preoperatively 3 had not met the inclusion and 4 had met exclusion criteria, 7 were withdrawn by an investigator and 20 chose to exit the study. The investigators withdrew one participant each for cerebral disorder and ulcer in the CLGES

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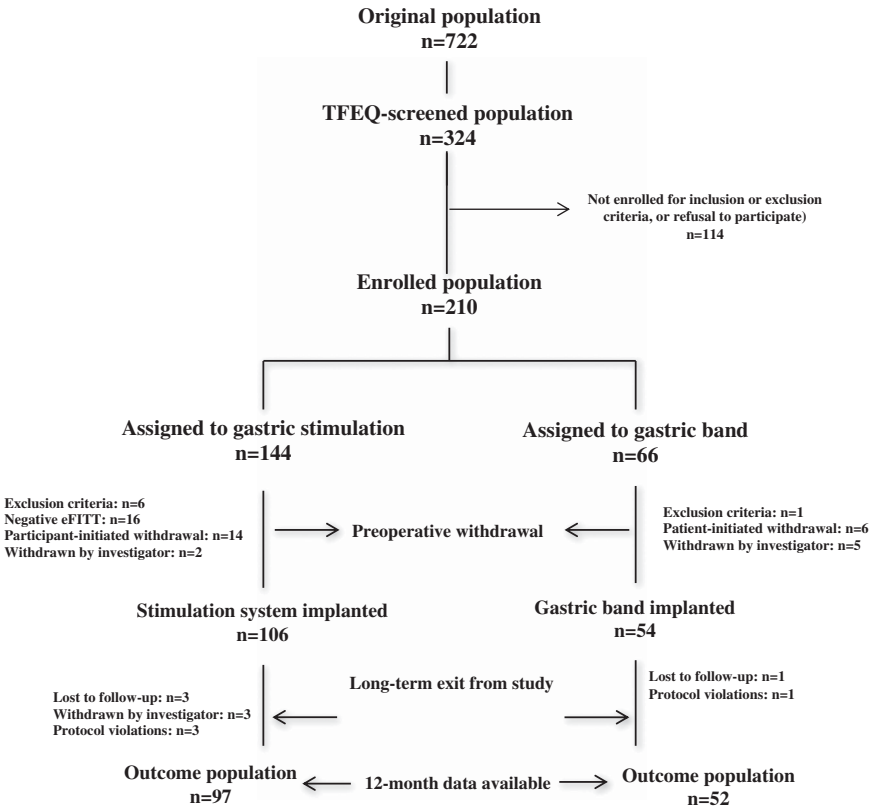

Figure 2. Flow of patients from screening to end of 12-month randomization period.

group, and one participant each for abdominal adhesions, hernia, cancer, ulcer and an unspecified illness in the LAGB group. Ultimately, 160 patients were randomly assigned to and were treated with CLGES ($n = 106$) versus LAGB ($n = 54$). The flow of patients between prescreening and the end of the study is shown in Figure 2. The mean age, weight and BMI of the 76 women and 30 men included in the CLGES group were 39 ± 11 years, 121 ± 21 kg and 42 ± 5 kg m^{-2}, respectively, whereas those of the 44 women and 10 men in the LAGB group were 39 ± 12 years, 123 ± 20 kg and 44 ± 6 kg m^{-2}, respectively. The characteristics of both study groups are detailed in Supplementary Table 3 of the Supplementary Material; all between-groups differences are statistically non-significant.

Between discharge of the patients from the hospital and the 12-month follow-up, 6 patients (5.7%) in the CLGES group and 1 (1.9%) in the LAGB group exited the study. Three patients in the CLGES and 1 in the LAGB group entered the study even though they did not satisfy the entry criteria, and were also excluded. The final outcomes were ascertained of (a) 97 patients treated with CLGES (91.5%) and 52 (96.3%) treated with LAGB who completed the 12-month study, and (b) the full analysis set population.

Weight loss at 12 months

In the patients who completed the study, the 12-month %EWL in 97 patients initially assigned to CLGES was 35.1, versus 40.0% in 52 patients assigned to LAGB (NS). In the full analysis set, at last follow-up, the decrease in EWL was similar in both study groups, whereas the changes in BMI and %WL were greater in the LAGB group (Table 1A). In the CLGES group, 74.5, 61.3 and 41.5% of patients reached $\geqslant 20$, $\geqslant 25$ and $\geqslant 35$% EWL, respectively, whereas 28.3% of patients reached < 20% EWL (Table 1B). Although the percentages of patients meeting each end point were ~10% higher in the LAGB than in the CLGES group, these differences

Table 1. Weight loss (A) and percent of patients who lost from < 20% to $\geqslant 50$% of excess weight loss (B), up to 12 months in each group of the full analysis set

	Gastric stimulation (n = 106)	*Gastric band (n = 54)*	P-*value*
A. Weight loss measures			
Decrease in			
Body mass index, kg m^{-2}			
Month			
3	3.7 ± 2.4	4.3 ± 1.9	NS
6	4.7 ± 3.2	6.1 ± 2.8	0.01
12	5.3 ± 3.8	7.0 ± 3.8	0.01
Weight			
Month			
3	8.8 ± 5.4	9.9 ± 4.4	NS
6	11.0 ± 7.1	14.0 ± 6.2	0.01
12	12.5 ± 8.2	16.0 ± 8.5	0.01
Excess weight			
Month			
3	22.9 ± 15.6	24.7 ± 13.3	NS
6	28.7 ± 20.0	34.2 ± 17.0	NS
12	32.1 ± 21.7	39.0 ± 22.9	NS
B. Percent of patients who lost: % excess weight loss			
< 20	28.3 (19.8–36.9)	18.5 (11.1–25.9)	NS
$\geqslant 20$	74.5 (66.2–82.8)	81.5 (74.1–88.9)	NS
$\geqslant 25$	61.3 (52.0–70.6)	72.2 (63.7–80.7)	NS
$\geqslant 35$	41.5 (32.1–50.9)	53.7 (44.2–63.2)	NS
$\geqslant 50$	19.8 (12.2–27.4)	29.6 (20.9–38.3)	NS

Values are means ± s.d. or percentages (95 confidence interval).

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were not statistically significant (Supplementary Figure 1 of Supplementary Material). Similarly, 19.8% of patients in the CLGES and 29.6% in the LAGB group achieved ⩾50% EWL (NS). Finally, the 3 criteria of the composite end point were reached by 73.0% of patients in the CLGES versus 66.7% in the LAGB group (Supplementary Table 4 of Supplementary Material). This −6.3% difference (upper 95% CI = 7.2%) between the two study groups satisfied the non-inferiority hypothesis. Furthermore, 65 of 97 patients (67%) who were initially randomized to CLGES and completed the 12-month study, reached the additional efficacy end point of a ⩾25% EWL (lower limit of two-sided 95% CI = 56.6%; $P < 0.001$). This additional efficacy end point was also met by 65 of 106 patients (61%) in the full data sets of the CLGES group (lower limit of two-sided 95% CI = 52.0%; $P < 0.001$).

Secondary efficacy end points

The changes in QOL, using the IWQOL-Lite and BDI-II questionnaires, in eating behavior using the TFEQ, and in several other secondary efficacy end points are shown for the entire sample in Supplementary Table 5A and for the subgroups of patients presenting with cardiovascular risk factors in Supplementary Table 5B. QOL improved significantly and similarly in both groups (Figure 3a). It is, however, noteworthy, that the mean BDI-II questionnaire score was significantly lower at 6 months than at baseline in both study groups, and remained significantly lower at 12 months in the CLGES group only, whereas it returned toward baseline in the LAGB group (Figure 3b). The changes in eating behavior between baseline and 12 months (Supplementary Figures 2A–C of Supplementary Material) were statistically significant and similar in magnitude in both groups.

Changes in patients presenting with cardiovascular risk factors

In the subgroup of patients presenting with cardiovascular risk factors, the baseline blood concentration of HbA1c was ⩾6% in 14 patients in the CLGES and 10 in the LAGB group. A 6–7% decrease in HbA1c was observed at 12 months in both groups. Total cholesterol was $>200\ \text{mg dl}^{-1}$ at baseline in 34 patients in the CLGES group and 22 patients in the LAGB group. A significantly greater decrease ($P < 0.05$) in total cholesterol was measured at 12 months in the CLGES than in the LAGB group in the entire sample as well as in the subgroups presenting with elevated baseline blood cholesterol concentrations. The changes in low- and high-density lipoprotein cholesterol, serum triglycerides and systolic and diastolic blood pressure were similar in both groups. The changes in all the cardiovascular risk factors in the entire sample, as well as in the subgroups with baseline comorbidity are reported in Supplementary Tables 5A and B.

Safety analysis

The mean duration of surgical implantation of the CLGES was 58 ± 17 min (range 33–110), versus 64 ± 21 min (range 24–100) for the LAGB (NS). The AE that occurred in each study group during the 12 months of follow-up are shown in Table 2. A persistent intolerance to liquids, and a re-operation for slippage of the band were two major perioperative AE that occurred in the LAGB group. Minor perioperative AE occurred in 6 patients in the CLGES group, consisting of hypotension, incomplete wound healing, painful surgical scar and nausea and belching, and in 2 patients in the LAGB group, who complained of belching and general discomfort, respectively. Over the long-term, 15 minor and 37 moderate or major AE were recorded in the CLGES, versus 38 and 66, respectively, in the LAGB group (Table 2). The proportion of patients who experienced an AE was significantly lower in the CLGES (34%) than in the LAGB (81%) group (Δ = −47%; 95% CI −61% to −33%; $P < 0.001$; Figure 4). The proportion of patients who suffered major device-related adverse events was 4.7% in the CLGES versus 13.0% in the LAGB group (NS). No participant died during the 12-month follow-up in either group.

DISCUSSION

Main study findings

Our study is the first randomized comparison of the 1-year safety and efficacy of CLGES versus LAGB in a large sample of morbidly obese patients. Its results indicate that the minimally invasive, laparoscopic CLGES system produced a similar, significant and sustained weight loss, as the LAGB, though at the cost of significantly fewer AE. Furthermore, a greater decrease in total cholesterol and a sustained alleviation of depression were observed at 12 months in the CLGES group, in contrast with the

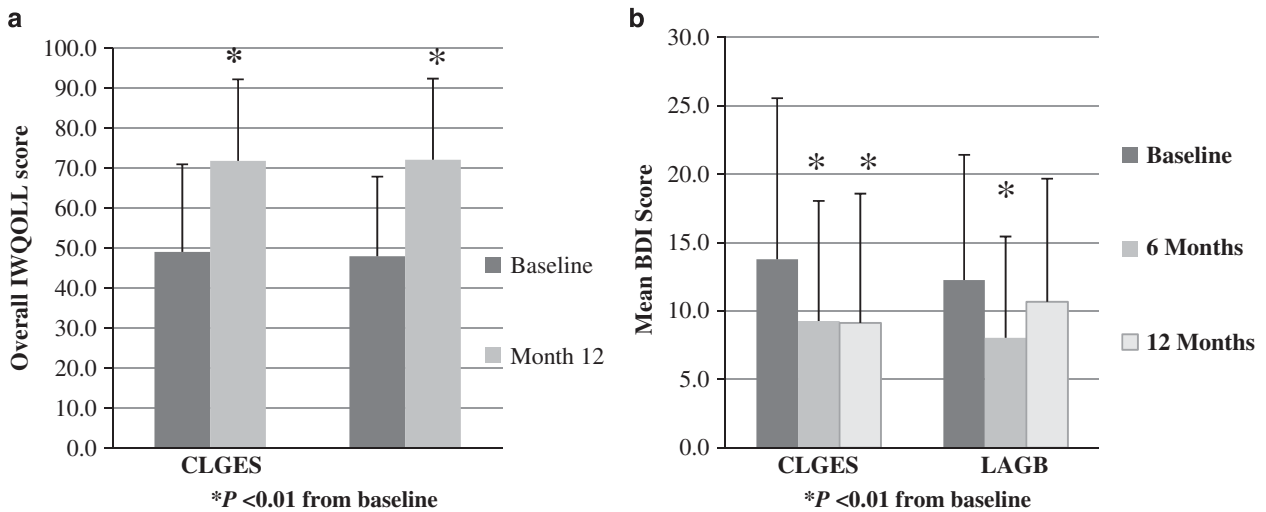

Figure 3. (**a**) Change in total IWQOL-LITE score between baseline and 12 months in each study group. The change is statistically significant in both groups; however, the between-groups difference at 12 months is not statistically significant. (**b**) Change in BDI-II score between baseline and 6 and 12 months in both study groups. It is noteworthy that, although the score decreased significantly between baseline and 6 months of follow-up in both study groups, it remained significantly lower ($P < 0.01$) at 12 months in the CLGES group, while it returned toward baseline and was no longer significantly lower at 12 months in the LAGB group.

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Table 2. Numbers of patients who experienced ⩾1 device- or procedure-related adverse events during 12 months of follow-up in each study group

	Gastric stimulation n = *106*	*Gastric band* n = *54*	P-*value*
Perioperative adverse events	6 (6)	4 (7)	NS
Long-term adverse events			
Gastrointestinal			
Nausea/vomiting	4 (4)	31 (57)	< 0.001
Dysphagia/restriction	0	16 (30)	< 0.001
Dyspepsia/acidity	0	10 (19)	0.002
Epigastric discomfort	0	4 (7)	< 0.05
Body as a whole			
Anxiety	0	3 (6)	NS
Hair loss	0	9 (17)	0.003
Musculo-skeletal discomfort	15 (14)	3 (6)	NS
Device/system dysfunction			
Miscellaneous	4 (4)	7 (13)	NS
Painful stimulation	8 (8)	NA	-
Surgical pocket discomfort	8 (8)	NA	-
Device replacement/lead fracture	4 (4)	NA	-
Explant for Twiddler Syndrome	1 (1)	NA	-
Band slippage	NA	1 (2)	-
Port revision	NA	2 (4)	-
Pouch dilatation	NA	1 (2)	
All long-term device- or procedure-related adverse events	44	87	< 0.001

Values are numbers (%) of observations; patients who experienced > 1 AE were counted only once.

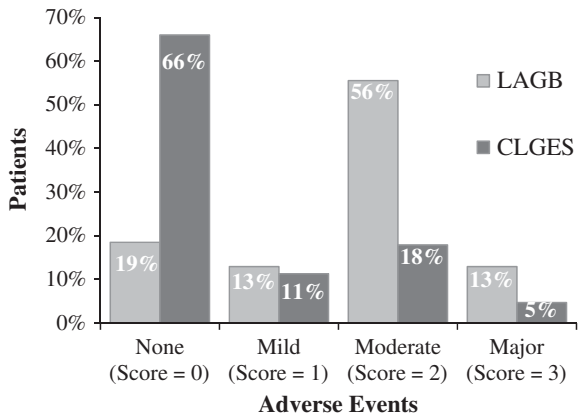

Figure 4. Proportions of patients who suffered AE in each study group. A score was assigned (0 = none, 1 = mild, 2 = moderate, 3 = major), reflecting the most severe AE experienced by each patient. The Mann–Whitney *U*-test was used to compare the severity of AE in each group. The CLGES group experienced significantly fewer and less severe AE ($P < 0.001$).

LAGB group, where the 12-month serum cholesterol concentration and BDI-II score returned toward baseline values.

The most noteworthy observation made in this randomized comparison, however, was the significantly and markedly lower rate and severity of long-term AE recorded with the CLGES. Despite their classification as 'minor' or 'moderate', the frequent occurrence of symptoms, such as nausea, vomiting, dyspepsia, dysphagia, belching and other complications of LAGB, interferes prominently with daily life and may have major repercussions on the patient's mood and mental stability, as evidenced by the BDI-II scores in the LAGB group. The 56% of patients treated with LAGB who developed moderate, device-related AE in this study is similar to the 61 and 48% reported in two Premarket Approval Applications for LAGB systems.[21,22] The average number of fills per patient was: 2.1 in the first year, and average number of deflations per patient was 0.6. We observed no correlation between average number of inflations and either weight loss or adverse events.

Furthermore, in contrast to LAGB, which imposes considerable limitations to the types of food that can be consumed,[28] patients who have undergone CLGES are free to eat what they want and are allowed to lose weight without mechanical restriction. Instead, they learn to recognize satiety and develop healthy eating habits from the feedback of the sensor. Such behavioral reinforcement of habits is critical to the long-term maintenance of weight loss and control of concomitant disorders.[29]

Role of gastric electrical stimulation

The invasive nature and complications associated with bariatric surgery have considerably limited the proportion of patients who are eligible to undergo these procedures.[30] Therefore, various attempts have been were made to develop less invasive and non-permanent techniques of weight management. Gastric Electrical Stimulation to treat obesity began with animal experiments, nearly 20 years ago, by Cigaina *et al.*[31] Multiple experimental and clinical studies of GES, recently reviewed in detail by Cha *et al.*[13] have been performed with encouraging results, using different stimulation and delivery characteristics, all designed to control food intake. The therapy systems tested have had differing physiological targets for the stimulation: the gastric antrum,[32,33] the anterior lesser curvature where the vagus innervates the stomach,[34,35] and directly on the abdominal vagal branches.[36] The systems also have different proposed mechanisms of action. The vBloc (EnteroMedics Inc., St Paul, MN, USA) therapy has reported the best clinical weight loss results of the three systems evaluated for treating obesity. Although vBloc did not meet the primary end points in a randomized, double-blind study,[36] at 18 months the EWL was stable at 26% and significantly different from sham.[37] The differences in neural targets and stimulation parameters would at least partially explain the differences seen in clinical outcomes with the above systems. With both the Transcend system (Medtronic Inc., Minneapolis, MN, USA)[34] and vBloc therapies, stimulation was applied for ⩾12 h per day, probably causing neural habituation and loss of efficacy. We hypothesize that the greater weight loss with the CLGES system is attributable to the closed-loop trigger of stimulation by the food intake sensor, limiting the stimulation to an average of 3 h per day and minimizing the neural habituation. Additionally, the electrical stimulation parameters were tailored to the individual to produce the desired gastric symptoms at initial programming, and at follow-ups. Another distinct advantage of the CLGES system over other systems is the absence of need to recharge the power supply, preventing the patients from interfering with the delivery of therapy.

Choice of comparative treatment method

We chose LAGB as a comparative treatment method as it is, like CLGES, a reversible, minimally invasive procedure. Although the main putative mechanism of LAGB is a mechanical restriction of the food passage through the proximal stomach, it has been hypothesized that satiety is caused by vagal afferent stimulation, itself induced by distension of the proximal segment of the stomach.[38] Therefore, CLGES and LAGB might both stimulate vagal autonomic nervous activity, the former directly, without mechanical restriction.

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Limitations of our study

An important limitation of this study was the inability to blind the randomization process, for evident reasons related to the nature of the treatment interventions. Furthermore, the gastric stimulation sensitivity test (eFITT), used to withdraw patients insensitive to GES, was not used in the LAGB group. Since the eFITT is part of the usual management of candidates for CLGES therapy, the trial design faithfully reproduced standard clinical practice. We acknowledge that this design may have introduced a selection bias, though it closely emulated usual patient care. Third, the reliability of some comparisons made between the two study groups, particularly with regards to the comorbidities, may have been limited by small numbers of observations. Fourth, the durable effects of CLGES will need to be confirmed beyond the 1-year follow-up. Observations made after the end of the study revealed an average $37 \pm 21\%$ EWL at 18 months in the CLGES group.[39] On the basis of reported long-term results, LAGB therapy produces a maximum weight loss at 18 months, followed by a stable period before the resumption of weight gain.[40] The new characteristics of the CLGES system, including the tailoring of stimulation and the use of sensor data feedback will need to be optimized on the long term, with the view of preventing or mitigating the regain of excess weight observed with all bariatric therapies in the absence of actual lifestyle modifications.[41]

CONCLUSION

This 1-year, randomized trial confirmed the non-inferiority of CLGES compared with LAGB in the management of morbid obesity. Furthermore, a clinically meaningful and significantly lower rate of AE was observed in the CLGES- compared with the LAGB-treated patients.

CONFLICT OF INTEREST

Dr Horbach reports receiving personal fees from IntraPace for his services as a scientific advisor. He has received honoraria for proctoring and traveling expenses from Johnson & Johnson, Apollo, Torax and the German Society for Gastrointestinal Surgery. Dr Torres reports receiving personal fees from IntraPace for his services as a scientific advisor. He has received honoraria for proctoring and traveling expenses from Ethicon, Covidien and Gore. Drs Meyer, Morales, Alarcon, Favretti, Anselmino, Rovera, Susewind and Dargent have no potential conflict of interest to disclose. The sponsor, IntraPace Inc, funded the clinical sites for screening of the patients, testing, hospitalization, surgery (implant) and data management.

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