Obesity Surgery, 14, S33-S39

Progress in Implantable Gastric Stimulation: Summary of Results of the European Multi-Center Study

Maurizio De Luca[1]; Gianni Segato[1]; Luca Busetto[1]; Franco Favretti[1]; Franz Aigner[2]; Helmut Weiss[2]; Charles de Gheldere[3]; Giorgio Gaggiotti[4]; Jacques Himpens[5]; Jorge Limao[10]; Matthias Scheyer[7]; Mauro Toppino[8]; Ernst L. Zurmeyer[9]; Giorgio Bottani[10]; Heinrich Penthaler[11]

[1]Regional Hospital of Vicenza, Italy; [2]University Hospital Of Innsbruck, Austria; [3]H. Hart Hospital, Belgium; [4]University Hospital INRCA-IRCCS, Italy; [5]St.-Blasius Hospital, Belgium; [6]Egas Muniz Hospital, Portugal; [7]Krankenhaus der Stadt, Austria; [8]Ospedale Molinette, Italy; [9]Städisches Krankenhaus, Germany, [10]Asilo Vittoria, Italy; [11]Ospedale di Bolzano, Italy

Background: The Implantable Gastric Stimulator (IGS®), a pacemaker-like device, has been found to be safe and effective to induce and maintain weight loss. The LOSS (Laparoscopic Obesity Stimulation Survey) is a prospective non-randomized trial which enrolled 69 patients involving 11 investigator centers in 5 European Countries. In 19 patients, ghrelin was analyzed.

Methods: Between January 2002 and December 2003, 69 patients (F/M 49/20), mean age 41 years (18-65) underwent IGS implantation. Mean BMI was 41 (35-57), mean weight 115.0 kg (65-160) and mean excess weight (EW) 52 kg (13-89). The IGS was actived 30 days after implantation. In a subset of 19 patients studied further, 0, 6, and 12 months appetite and satiety score were evaluated and 0 and 6 months ghrelin profile was analyzed.

Results: The mean ± standard error %EWL was: 8.6±1.8 at 1 month, 15.8±2.3 at 3 months, 17.8±2.6 at 6 months, 21.0±3.5 at 10 months, and 21.0±5.0 at 15 months. There were no intraoperative surgical or long-term complications. 7 intra-operative gastric penetrations occurred, observed by gastroscopy, without sequelae. 1 patient required a reoperation to remove a retained lead needle. In the subset of 19 patients, appetite was reduced and post-prandial and inter-prandial satiety was increased after IGS implantation. In the 19 patients, despite weight reduction, ghrelin did not increase.

Conclusion: IGS can be implanted laparoscopically with minimal perioperative complications. Appetite is reduced and satiety is increased after the implantation. Ghrelin levels could be one of the mechanisms explaining weight loss and weight maintenance in IGS patients. If weight loss is maintained, IGS could be considered a good option for selected patients.

Key words: Obesity, device, implantable gastric stimulator, laparoscopy, weight loss, ghrelin

Correspondence to: Maurizio De Luca MD, Department of Surgery (Director: Franco Favretti), Regional Hospital of Vicenza, Contrà Pusterla n. 3, 36100 Vicenza, Italy. Fax: (+39) 0444 992482; e-mail: nnwdel@tin.it

Introduction

Obesity is a global problem, affecting an estimated 300 million individuals worldwide and causing an enormous economic burden. Many health problems such as insulin resistance, diabetes, hypertension, GERD, cardiovascular disease, cancer and sleep apnea are associated with obesity.

A new bariatric procedure, gastric myoelectrical stimulation, has been developed. The Implantable Gastric Stimulator (IGS®) induces satiety, while avoiding the morbidity and the mortality of the common restrictive, malabsorptive or combination restrictive/malabsorptive operations. The procedure does not alter the normal anatomy. Advantages of IGS are simplicity, a safer and more rapid proce-

dure, and a lack of nutritional side-effects associated with some bariatric operations.[1-5] The safety and efficacy of this form of therapy is being evaluated in the Laparoscopic Obesity Stimulation Survey (LOSS), a European prospective non-randomized clinical trial involving 69 patients in 5 countries (Italy, Austria, Germany, Belgium and Portugal).

Methods

Between January 2002 and December 2003, 69 patients (F/M 49/20) with mean age 41 years (18-65), underwent IGS implantation. Mean BMI was 41 (35-57), mean weight 115.0 kg (65-160), and mean excess weight (EW) 52 kg (13-89). The LOSS involved 11 investigator centers located in 5 European Countries (Table 1). All subjects gave signed informed consent for the operation and to enter this prospective non-randomized study.

The device consists of a stimulation lead implanted in the gastric wall, connected to an electronic pulse-generator (Transcend IGS®, Transneuronix Inc., Mt. Arlington, NJ, USA) which is implanted subcutaneously.

In 19 patients of the LOSS (Vicenza subset of patients), appetite and satiety scores were evaluated. These patients were asked to quantify their pre-prandial appetite, post-prandial satiety and inter-prandial satiety with the three separate 0- to 10-point visual scales before the procedure and at different times after implantation. In this subset, the baseline data were compared with the data obtained 6 months after IGS implantation, a period of time long enough to virtually exclude the persistence of a placebo effect. Moreover, these patients underwent a 12-month retrospective test in order to evaluate their last 12 months pre-prandial appetite, post-prandial satiety and inter-prandial satiety.[6]

Active ghrelin concentrations were evaluated in the subset of 19 morbidly obese patients of the LOSS (Vicenza subset of patients) before and 6 months after the implantation of the electrical gastric stimulator. Our protocol for ghrelin profiling required seven hourly blood samples for the measurement of ghrelin, starting from 07:00 hrs in fasting state, and continuing up to 14:00 hrs. A light Italian breakfast was served after the 08:00 hrs sample, and a complete lunch was served at noon. Active plasma immunoreactive ghrelin was measured using a highly-specific commercially-available RIA method by Linco Research[7].

Surgical Procedure

The lead was implanted by laparoscopy (by a 3 or 4 trocar access) on the lesser curvature at the end of the pes anserinus area, 6 cm proximal to the pylorus. The lead was fixed with 2 clips distally to avoid dislodgment, as seen in previous studies. Proximal fixation of the lead was sutured by EndoStitch® (Tyco).

One trocar access, through which the lead was extracted, was enlarged and a supra-fascial pocket was created. The generator was connected (proper connection was confirmed via radio-frequency programming), and then was implanted on the fascia and fixed by 2 sutures.

Table 1. Clinical sites of investigating centers

Site	Location	Investigator	Cases
Regional Hospital of Vicenza	Vicenza, Italy,	F. Favretti	20
University of Innsbruck	Innsbruck, Austria	F. Aigner	12
St. Blasius Hospital	Dendermonde, Belgium	J. Himpens	8
University Hospital INRCA	Ancona, Italy	G. Gaggiotti	8
Stadisches Krankenhaus	Ludwigshafen, Germany	E. L. Zurmeyer	6
Molinette Hospital	Turin, Italy	M. Toppino	6
Egas Muniz Hospital	Lisboa, Portugal	J. Limao	4
Hospital of Bolzano	Bolzano, Italy	H. Pernthaler	2
Krankenhaus der Stadt	Bludenz, Italy	M. Scheyer	1
H. Hart Hospital	Lier, Belgium	C. de Gheldere	1
Asilo Vittoria	Mortara, Italy	G. Bottani	1

During the laparoscopic operation to implant the IGS, the gastric mucosa was checked by gastroscopy. This is mandatory in order to exclude inadvertent needle perforation into the gastric lumen. In the event of perforation, the electrode lead is withdrawn and repositioned in an adjacent location. Gastroscopy is than repeated. The gastroscopy also establishes the distance between the electrodes and the relationship to the cardia or pylorus. Mean surgery time was 58.5 min (37-85).[6]

Patient Selection

Patient inclusion criteria are shown in Table 2, and exclusion criteria are listed in Table 3.

Postoperative Management

Following surgery, the lGS was switched to the 0FF setting, to permit the gastric tunnel to heal. An upper GI barium study was performed prior to discharge to confirm that there was no leak and to document the immediate postoperative lead location. Electrical activation was at 1 month following implantation. The stimulation parameters used when the device is activated 1 month after operation are shown in Table 4.

The patients were requested to appear for follow--up at intervals as shown in Table 5.

Statistical Analysis

Data were entered into Microsoft Excel (Microsoft, Redmond, WA, USA) or Statview (Abacus Concepts). Weight loss is expressed as percent excess weight loss (%EWL). Comparison of weight change between males and females was by Chi-square analysis for categorical variables. A *P*-value <0.05 was considered significant.

Table 2. Inclusions criteria

Age: 18-65 years.
Use of adequate birth control methods.
BMI 35-40 with documented co-morbidity or 40-45.
Able and willing to travel to the clinical site for designated follow-up.

Table 3. Exclusion criteria

- Pregnant or lactating females.
- Prior surgery of GI tract as therapy for obesity.
- Prior surgery on the stomach for any reason.
- Other implanted electro-stimulation device.
- Untreated active gastric ulcer or at high risk for developing gastric or duodenal ulcer.
- Any weight loss medication.
- Required continuous therapy with known ulcerogenic medication (e.g., aspirin and non-steroidal anti-inflammatory agents NSAIDs).
- History of cardiac arrhythmia or severe cardiac disease (NYHA class III or IV).
- Severe weight related co-morbid diseases that require immediate weight loss (e.g., life-threatening sleep apnea).
- Patients with any serious health condition not related to their weight.
- Patients who the physician considers to be unable or unwilling to fulfil requirements of this survey.
- Use of an investigational agent or device within 30 days prior to implant.

Results

The mean ± standard error (SE) of %EWL are shown in Table 6 and Figure 1. %EWL was: 8.6±1.8 (SE 0.91±1.2) at 1 month, 15.8±2.3 (SE 1.38±2.1) at 3 months, 17.8±2.6 (SE 1.98±2.3) at 6 months, 21.0±3.5 (SE 2.64±2.6) at 10 months, and 21.0±5.0 (SE 3.78± 2.9) at 15 months.

Table 4. Stimulation parameters used in the Laparoscopic Obesity Stimulation Survey (LOSS)

The IGS® was actived 30 days after implantation

- Pulse Amplitude: 10.0 mA
- Pulse Width: 208 microsec
- Burst Rate: 40 Hz
- Time Burst On: 2 sec.
- Time Burst Off: 3 sec.

At month 6, the Pulse Amplitude was increased to 12.2 mA and the Pulse Width to 650 microsec and turned off overnight (varying patient to patient).

Table 5. Follow-up schedule after IGS implantation

1st Year: Month 1, 2, 3, 4, 6, 8, 10, 12
2nd Year: Month 3, 6, 9, 12
3rd Year: Month 6, 12

Table 6. Results (Mean %EWL)

Month	0	1	3	6	10	15
N	69	63	57	51	43	20
%EWL	0	-8.6	-15.8	-17.8	-21	-21
S. E.	0	0.91	1.38	1.98	2.64	3.78

S. E. = standard error

There were 7 intra-operative gastric penetrations, observed by gastroscopy; in these cases, the electrode was withdrawn and repositioned in an adjacent location, always on the lesser curvature at the end of the pes anserinus area.

One patient required a reoperation to remove a retained lead needle. There were no other immediate peri-operative complications. No lead dislodgement was seen on the first postoperative day abdominal X-ray, nor in the following months on the lead impedance test.

One patient presented during the first postoperative month with pain at the abdominal stimulator site. This symptom was reduced with NSAIDs.

Results of pre-prandial appetite and post-prandial and inter-prandial satiety visual scale score of 19 subjects (the Vicenza subset patients of LOSS) evaluated at baseline and at 6 months after implantation[13] are shown in Table 7.

Results of the retrospective test in 19 subjects (the Vicenza subset patients) in order to evaluate their last 12 months pre-prandial appetite, post-prandial satiety and inter-prandial satiety[6] are shown in Table 8.

The 7-hour plasma ghrelin profiles in 19 subjects (the Vicenza subset patients) treated with gastric stimulation at baseline and 6 months after IGS implantation are shown in Table 9. Despite weight loss, the hourly ghrelin profiles showed a reduction of ghrelin levels in most of the hourly measurements. Neither fasting ghrelin levels nor the area under the ghrelin curve changed significantly after IGS. This demonstrates that the weight loss produced by gastric electrical stimulation was not accompanied by the increase in ghrelin levels that usually occurs with caloric restriction.

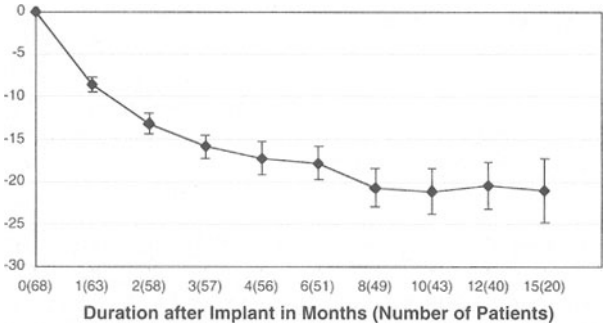

Figure 1. Mean % excess weight loss (± standard error).

Discussion

The Implantable Gastric Stimulator (lGS®) induces satiety while avoiding the morbidity and mortality of the common restrictive, malabsorptive or combination restrictive/malabsorptive operations. The procedure does not alter normal anatomy. Advantages of IGS therapy are simplicity, a safer and more rapid procedure, and a lack of nutritional side-effects that are associated with some bariatric operations.[6,8-11]

The Laparoscopic Obesity Stimulation Survey (LOSS), the European prospective non-randomized clinical trial involving 69 patients in 5 countries, evaluated the safety and efficacy of the IGS. These preliminary results confirm that laparoscopic implantation of the IGS is safer and more rapid than any other bariatric procedure, and had no perioperative complications.

No peri-operative or long-term dislodgement was observed in the LOSS group of patients. Distal fixation of the lead with 2 clips and proximal fixation by EndoStitch® (Tyco) was enough to avoid the dislodgement which occurred in a previous study.[6]

The data suggest that IGS, like other bariatric procedures, induces a most marked weight loss earlier in the postoperative course, but after a typical period of established weight loss, the %EWL continues to increase. In fact, some patients began to lose weight (with a firm sensation of satiety) at the 6th postoperative month. At month 6, the pulse amplitude of the generator was increased from 10.0 mA to 12.2 mA and the pulse width from 208 microseconds to 650 microseconds and turned off overnight (varying patient to patient).

In the LOSS study, a subset of patients were asked to quantify their pre-prandial appetite, post-prandial satiety and inter-prandial satiety with the three sep-

Table 7. Appetite and satiety scores in 19 patients before and after IGS.

Months	Pre-prandial Appetite	Post-prandial Satiety	Inter-prandial Satiety	No. of meals
0	6.9±2.0 (3-10)	1.3±2.0 (0-7)	3.8±2.8 (0-10)	3.4±1.2 (2-6)
1	4.3±3.3**	8.5±2.5***	6.8±3.2*	2.5±0.5**
2	5.7±3.1	3.2±4.1*	7.0±2.9**	2.1±0.3***
3	4.0±2.9***	7.6±3.0***	7.2±2.8**	2.3±0.5**
4	4.8±1.9**	7.1±2.7***	5.5±3.0*	2.2±0.4***
6	4.7±1.7** (0-8)	7.6±2.6*** (0-10)	6.1±2.2** (3-10)	2.1±0.3*** (2-3)

Before vs After IGS: *P <0.05; **P <0.01; ***P <0.001.

arate 0- to 10-point visual scales before the procedure and at different times after the implant procedure. In the 19 patients of this Vicenza subset group, the baseline data were compared with the data obtained 6 months after IGS implantation, a period of time long enough to virtually exclude the persistence of a placebo effect. In the visual scale, the pre-prandial appetite was significantly reduced and both post-prandial and inter-prandial satiety were significantly increased with gastric stimulation. Moreover, in the test evaluating satiety and appetite at baseline and 12 months after IGS implantation in the 19 patients, 68.4% observed a decrease in appetite before the meals, 89.4% an increase of satiety between meals, and 84.2% an increase in satiety after meals. Therefore, we can conclude that IGS therapy is able to produce an anorexigenic effect in obese patients. Weight loss is the consequence of this positive effect on the craving for food.

The exact mechanism of action of electrical stimulation therapy for obesity remains to be defined. Cigaina, in a preliminary study in animals, proved that chronic myo-electrical gastric stimulation was followed by reduced food intake and weight loss in swine.[2] Ouyang considered that a local electrical overdrive could affect the motor response of the antrum, causing a perturbation of normal gastric peristaltic activity.[12] Chronic gastric electrical stimulation was found to have an inhibitory effect on gastric slow peristaltic waves in the postprandial state in dogs.[13] Phillips showed that alterations of normal gastric peristalsis could decrease the rate of gastric emptying and increase gastric distension, a known satiety signal.[14] Electrical stimulation of the parasympathetic plexus of the muscle layers of the stomach could affect satiety through modifications of concentrations of the digestive neuro-hormones known to be involved in food intake regulation. Subtle changes of the meal-related responses of cholecystokinin and somatostatin and basal levels of glucagon-like peptide-1 after IGS have recently been reported.[10]

Table 8. Satiety and appetite in 19 Patients treated with gastric stimulation (12 months)

Decrease of appetite before meals	68.4% (13 patients)
Increase of satiety between the meals	89.4% (17 patients)
Increase of satiety at the end of the meals	84.2% (16 patients)

Ghrelin is an orexigenic hormone discovered in 1999. It is to date the most potent orexigenic signal produced by the GI tract. When secreted in the bloodstream, it reaches the hypothalamic centers, where it stimulates food intake.[15] Interestingly, the ghrelin pathway and the vagal pathway are not independent from one another. In animals, electrical stimulation of the vagus nerve tends to decrease ghrelin levels, and in humans, the mastication of food without ingestion (a protocol for testing gastric vagal stimulation and the cephalic phase of food intake) exaggerates the normal post-prandial suppression of ghrelin levels.

Table 9. Ghrelin levels in 19 patients before and after IGS

Hours	BEFORE IGS		AFTER IGS	
07:00 breakfast	65.0±35.2	(36.4-152.4)	65.3±47.8	(30.5-231.7)
08:00	71.4±38.5	(39.1-173.7)	72.4±65.4	(23.7-317.4)
09:00	80.4±43.2	(42.5-160.4)	66.0±41.6	(26.3-199.9)
10:00	94.7±67.8	(41.1-269.9)	79.8±48.1	(30.6-215.7)
11:00	109.5±75.2	(49.7-280.7)	109.4±74.4	(35.5-328.6)
12:00 lunch	118.8±76.3	(48.1-296.3)	105.7±58.4	(52.6-259.4)
13:00	98.4±62.4	(40.8-282.9)	94.0±47.7	(45.3-248.7)
14:00	103.3±61.9	(40.4-227.7)	95.6±75.0	(35.3-356.9)
AUC	657.5±386.9	(332.9-1627.0)	607.8±374.5	(265.8-1864.1)

1 patient refused to repeat the ghrelin profile after IGS.
Before vs After IGS: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.
AUC = area under a ghrelin curve.

Ghrelin is produced primarily by cells in the oxyntic glands of the stomach. The expression of the peptide is stimulated by fasting and suppressed by food intake. Several observations from both animal and human studies suggest that ghrelin has the unique capacity to influence meal initiation. Moreover, human plasma ghrelin levels increase sharply before every meal and decrease after every meal. The role of ghrelin in the long-term regulation of food intake is supported by the evidence that continuous or repeated ghrelin administration increases body weight.[7]

Cummings et al[15] compared 24-hour ghrelin profiles from 13 human subjects before and after dietary weight loss (average weight loss 17.4%) and found that circulating ghrelin levels increased after the diet-induced weight loss. This finding is consistent with a role for ghrelin in long-term regulation of weight in humans. These observations are particularly important for the therapy of obese patients because they could explain, at least in part, the compensatory increase in appetite before and after meals that contributes to the poor long-term maintenance of weight loss achieved by caloric restriction.[15]

In our study on the subset of 19 patients, we found that, despite EWL of 6.8% over 6 months, fasting ghrelin levels did not change after IGS (65.0 picogram/ml vs 65.3 picogram/ml), and the ghrelin profile on hourly measurement showed a small non-significant reduction. Because no significant correlations between the changes in ghrelin levels and the degree of weight loss were observed in our sample, this could explain the stable loss of appetite and the long-term maintenance of weight loss observed in patients with gastric stimulation.

It is important to identify the features of a selected group of patients to implant the IGS. At the moment, the selection of a specific restrictive or malabsorptive operation is usually related to the experience of each bariatric surgical group, which varies by country.[16] The long-term weight loss efficacy and risk-benefit and cost-benefit ratios of the IGS will eventually need to be compared with existing bariatric operations. The selection of the patients involves alimentary habit, psychological condition, gender (according to some studies), anatomical weight distribution (android or gynoid), influence of preexisting co-morbid conditions, and degree of obesity. Our series did not observe different results in the two genders, but follow-up is short.

Conclusion

Preliminary data of LOSS showed that IGS can be safely implanted laparoscopically. The operation was easier to perform than other bariatric procedures. Studies indicate minimal peri-operative complications, and no side-effects have been observed from gastric stimulation therapy.

LOSS is evaluating weight loss over time. If the weight loss is maintained, the IGS could be considered as the first choice operation in the treatment of morbid obesity. IGS is not indicated as a second choice procedure after restrictive or malabsorptive operations.

References

1. Cigaina V, Saggioro A, Rigo V et al. Long-term effects of gastric pacing to reduce food intake in swine. Obes Surg 1996; 6: 250-3.
2. Cigaina V, Saggioro A, Pezzangora V. The long-term effects of gastric pacing on an obese young woman. Obes Surg 1996; 6:312-3 (abst 41).
3. Cigaina V, Pinato GP, Rigo V et al. Gastric peristalsis control by mono situ electrical stimulation: a preliminary study. Obes Surg 1996;6:247-9.
4. Cigaina V, Adler S, Rigo V et al. Implantable gastric stimulator (IGS) as therapy for morbid obesity: equipment, surgical technique and stimulation parameters. Obes Surg 1999; 9: 357-8 (abst 136A).
5. Cigaina V, Saggioro A, Gracco L et al. Gastric pacemaker to treat morbid obesity - five year experience. Obes Surg 2001; 11: 171 (abst P8).
6. Favretti F, De Luca M, Segato G et al. Treatment of morbid obesity with the Transcend® Implantable Gastric Stimulator (IGS®): A prospective survey. Obes Surg 14, 2004: 666-70.
7. Busetto L, De Luca M, Favretti F et al. Ghrelin levels before and after weight loss in morbidly obese patients treated by an implantable electrical gastric stimulator. JAMA (in press).
8. D'Argent J. Gastric electrical stimulation as therapy of morbid obesity: preliminary results of the French study. Obes Surg 2002; 12: 21S-25S.
9. McCallum RW, Chen JD, Lin Z et al. Gastric pacing improves emptying and symptoms in patients with gastroparesis. Gastroenterology 1998; 114: 456-61.
10. Cigaina V, Hirschberg A. Gastric pacing and neuroendocrine response: a preliminary report. Obes Surg 2000; 10: 334 (abst 89).
11. Xing JH, Brody F, Brodsky J et al. Gastric electrical stimulation at proximal stomach induces gastric relaxation in dogs. Neurogastroenterol Motil 2003; 15 (1): 15-23.
12. Ouyang H, Yin J, Chen JD. Therapeutic potential of gastric electrical stimulation for obesity and its possible mechanism: a preliminary canine study. Dig Dis Sci 2003; 48: 698-705.
13. Chen JD, Qian L, Ouyang H et al. Gastric electrical stimulation with short pulses reduces vomiting but not dysrhythmias in dogs. Gastroenterology 2003; 124: 401-9.
14. Phillips RJ, Powley TL. Gastric volume rather than nutrient content inhibits food intake. Am J Physiol 1996; 271: R766-R779.
15. Cummings DE, Weigle DS, Frayo RS et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med 2002; 346: 1623-30.
16. Favretti F, Cadiere GB, Segato G et al. Laparoscopic adjustable silicone gastric banding (Lap-Band®): How to avoid complications. Obes Surg 1997; 7: 352-8.