ORIGINAL RESEARCH

Endoscopic sutured gastroplasty in addition to lifestyle modification: short-term efficacy in a controlled randomised trial

Vincent Huberty ,[1] Ivo Boskoski ,[2] Vincenzo Bove,[2] Pauline Van Ouytsel,[1] Guido Costamagna,[2] Marc A Barthet ,[3] Jacques Devière[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-322026).

[1]Department of Gastroenterology, Hepatopancreatology and Digestive Oncology. Erasme Hospital, Université libre de Bruxelles (ULB), Brussels, Belgium
[2]Digestive Endoscopy Unit, Digestive Endoscopy Unit. Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[3]Gastroenterology, Hopital Nord, Marseille, France

Correspondence to
Dr Vincent Huberty, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology. Erasme Hospital, Université Libre de Bruxelles, Bruxelles 1070, Belgium; Vincent.Huberty@erasme.ulb.ac.be

MAB and JD are joint senior authors.

Received 30 May 2020
Revised 21 September 2020
Accepted 21 September 2020

To cite: Huberty V, Boskoski I, Bove V, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2020-322026

ABSTRACT

Objective Endoscopic suture gastroplasty (ESG) has been developed as an alternative treatment for moderately obese patients. We present our results of a short-term randomised controlled trial on a new suturing technique, the Endomina system (E-ESG, Endo Tools therapeutics, Belgium).

Design Eligible patients (body mass index 30–40 kg/m^2) were randomised in a 2:1 ratio to receive lifestyle modification plus E-ESG or lifestyle modification alone (control group); dietetic counselling and follow-up were identical. Endpoints included a mean excess weight loss (EWL) of more than 25% 12 months after E-ESG and a 15% EWL difference at 6 months between groups. At 6 months, a cross-over to E-ESG was offered to the control group. All patients were followed for a total of 12 months after E-ESG.

Results Of the 71 patients included (five male, mean age 40 years), mean EWL at 6 months was significantly higher in the treatment (38.6%, n=45) than in the control group (13.4%, n=21; p<0.001). At 6 months, satiety tests demonstrated a higher decrease in mean volume (41% vs 2.5%, p<0.001), and mean quality of life (QoL) was also higher in the treatment group (52.8 vs 45.1 p<0.05). No procedure-related or device-related severe adverse events were observed. Twelve months follow-up after E-ESG showed a mean EWL of 45.1%, which translated into a total body weight loss of 11.8%.

Conclusions This study demonstrates that E-ESG is safe and effective, providing a 25% better EWL at 6 months than lifestyle modification alone. This weight loss was maintained and resulted in a significant improvement in QoL up to 18 months after treatment.

Trial registration number NCT03255005.

Significance of this study

What is already known on this subject?

► Endoscopic suture gastroplasty (ESG) is an emerging treatment for obese patients. Two techniques are currently available, but none have been evaluated as yet in a randomised controlled study.

What are the new findings?

► This randomised controlled trial demonstrates that ESG with the Endomina platform is safe and effective, providing 25% more excess weight loss than lifestyle modification alone at 6 months.
► In the treatment group including cross-over cases, the weight loss was maintained at 1 year and resulted in a significant improvement in quality of life.

How might it impact on clinical practice in the foreseeable future?

► ESG could become an early alternative interventional therapy to be offered to moderately obese patients (class I and II).

INTRODUCTION

To date, only surgery has been proven to be effective in the treatment of obesity and obesity-associated complications.[1] Surgery is, however, associated with potentially severe complications and is performed in only a minority of morbidly obese patients. Endoscopic bariatric therapies (EBTs) have been developed with the purpose of offering a less invasive approach to a wider range of patients. Recently, endoscopic tissue apposition with suturing devices has been used for performing gastric restriction. Three techniques have been evaluated and/or used in clinical practice. The Incisionless Operating Platform (USGI Medical, Santa Barbara, USA—Primary Obesity Surgery Endoluminal (POSE) procedure) allows endoscopists to perform multiple single plicatures and demonstrated excellent results in postmarketing studies.[2] However, these results were less impressive, although significant, in a randomised sham-controlled trial.[3] Endoscopic sutured gastroplasty (ESG) was initially described using the Overstitch (Apollo Endosurgery, Austin Texas, USA), and this has been the most frequently performed procedure for the treatment of class I and II obesity with good results reported in post-marketing retrospective studies.[4] The Endomina System (Endo Tools Therapeutics SA, Gosselies, Belgium) is another system that is used for ESG (here E-ESG in this paper) that has been shown to be effective in a prospective multicentre study after up to 1 year of follow-up.[5] The aim of this prospective randomised controlled trial (RCTs) was to assess the efficacy of this technique in combination with lifestyle management compared with standard lifestyle management alone.

METHODS

Study design

Adult patients with class I and class II obesity were prospectively enrolled from two centres (Erasme Hospital, Brussels, Belgium, and Policlinico Gemelli Foundation, Rome, Italy). They were randomly assigned in a 2:1 ratio to undergo E-ESG with Endomina (treatment group, TG) plus lifestyle management or lifestyle management alone (control group, CG) for 6 months. All patients underwent a multidisciplinary evaluation similar to the one that is performed before standard bariatric surgery.

The TG underwent the procedure and was followed at 2 weeks, 1, 3, 6, 9 and 12 months. The CG underwent similar moderate intensity nutritional follow-up for the first 6 months and after switch to procedure (cross-over cases). Per protocol, patients from the CG were offered the E-ESG procedure after 6 months, regardless of the weight loss they achieved with lifestyle intervention.

Face-to-face dietetic consultations were performed all along the study. Patients were seen by a trained dietician. Dietary consultations were free of charge for all patients. Patients were prescribed a low-calorie highprotein diet and lifestyle counselling based on Belgian Association for the Study of Obesity (BASO) 2010 and American Society of Metabolic and Bariatric Surgery (ASMBS) 2013 guidelines.[6] Physical activity was promoted. Psychological support was added to follow up on a case-by-case basis when needed. Weight loss medications were not prescribed.

This study is an investigator initiated study. No payment was asked to patients for treatment and follow-up related to the study. EndoTools Therapeutics provided a grant (number 650152) covering in part the expenses for data management and dietary consultations and procedures. The material was provided free of charge by the company.

Patient baseline and postprocedure evaluations

After providing informed consent, all patients with a body mass index (BMI) between 30 and 40 kg/m2 underwent evaluation of potential comorbidities and laboratory assessments, a quality of life (QoL) evaluation using the Short Form 36 (SF36) questionnaire,[7] and a satiety test. The drinking satiety test (modified from a previously described version[8]) consisted of drinking, every 60 s, 30 mL of a protein-rich and high-calorie nutritional drink (Fortimel Energy (Nutricia) [1.5 kcal/mL). At the beginning of the test, and every 5 min thereafter, five symptoms (hunger, fullness, nausea, bloating and pain) were assessed on a 10-point-scale. The test was stopped and volume of intake calculated when « fullness » was reported by the patient to be at a level of 10, or if one of the other symptoms became unbearable. The SF 36 questionnaire and the drinking satiety test were done at baseline, 6 months of follow-up, and at 12 months postprocedure (see online supplemental appendix table 1 for inclusion/exclusion criteria).

Endomina procedure

Endomina is a triangulation platform that can be used with any flexible endoscope and a dedicated needle (TAPES, Endo Tools Therapeutics SA, Gosselies, Belgium) to create gastrointestinal sutures. The platform is inserted over guidewires into the stomach and can then be opened and tightened around the endoscope. This feature obviates the need to use an overtube and allows the endoscopist to assemble/detach the system when needed without having to withdraw the device. The Endomina comprises two channels and the endoscope channel is free for instrumentation. One therapeutic channel can be bent perpendicularly to the axis of vision allowing piercing under visual control.

Grasping forceps are used through the endoscope to pull the gastric tissue inside Endomina, and a dedicated needle (TAPES, Endo Tools Therapeutics SA, Gosselies, Belgium) is then used for tissue piercing. Each TAPES is loaded with two anchors connected by surgical suture, allowing creation of single or double plications (interrupted stitches). The anchors are then pulled towards each other using a snare until the formation of a tight serosa-to-serosa apposition.

Sutures were placed in the gastric body, starting from the incisura and going up to the fundo-gastric junction. Sutures were placed anterior to posterior (double plications) in a Z-pattern (ie, double layer suturing) to optimise stomach tubulisation (figure 1 and online supplemental video 1). Patients were treated under general anaesthesia and hospitalised overnight per protocol. After the procedure they received proton pump inhibitors (40 mg once a day for 3 month). On-demand butylhyoscinine bromide (10 mg) and alizapride (50 mg) up to six times a day were prescribed for ten days. Medications were given intravenously for the first 24 hours. Patients were kept on a liquid diet for 3 days after the procedure and then returned to solid food within ten days with the use of mashed food as transition.

Outcomes

The primary endpoint was mean excess weight loss (EWL) of more than 25% and total body weight loss (TBWL) of more than 5% maintained at 1 year, according to ASGE PIVI guidelines.[9] The secondary endpoint included the 6-month comparison between patients who had an endoluminal procedure plus nutritional counselling (TG) versus those with nutritional counselling

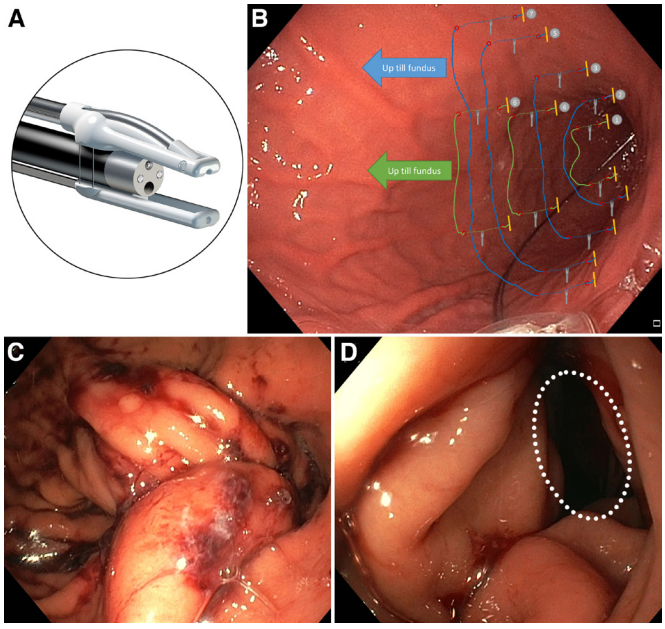

Figure 1 Illustration of E-ESG procedure. E-ESG, endoscopic suture gastroplasty with the Endomina platform. (A). Device around the scope (B) Endoscopic view before the procedure and suture pattern site to pull with forceps piercing point tag suture inside the stomach (inner line) suture outside the stomach (inner line) suture inside the stomach (outer line) placement sequence (C) Endoscopic view at end of the procedure showing gastric tubulisation (same scope position as in (b)) (D) Gastric lumen after tubulisation.

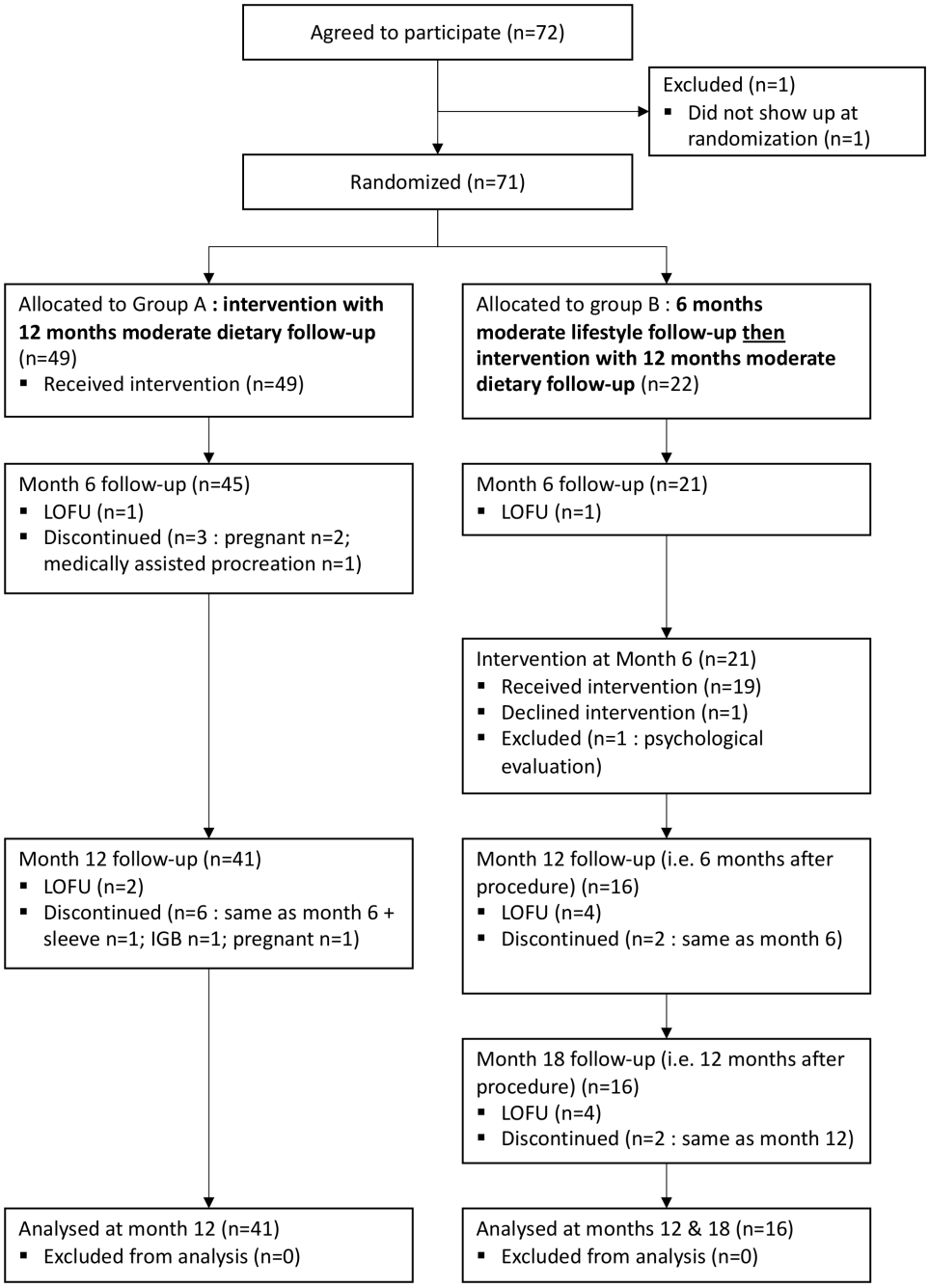

Figure 2 Flow chart. LOFU, lost of follow-up.

alone (CG). Other secondary endpoints included differences in QoL (SF36) at 6 and 12 months and differences in the drinking satiety test performed at baseline, 6 and 12 months.

Statistics

The sample size was estimated with a 80% power, 10% lost to follow-up, and a type 1 error of 0.05 based on both primary and secondary endpoint. For the primary endpoint, the number of patients was calculated at 40 for a mean EWL (%EWL) of more than 25% at 1 year (in the TG).

For the secondary endpoint (6 months comparison between treatment and CGs), assuming from our previous trial, at 6 months, a mean (SD) EWL of 41% (32%) and in the TG[10] and a mean (SD) EWL of 12% (22%) in the CG, calculated from the CG of previous RCTs as described by the American Society of Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable endoscopic Innovation (PIVI) Guidelines,[9] a total of 32 subjects (16 in each group) was required to achieve 80% power of detecting a treatment effect, with a significance level of 0.05 using a two-sided two sample t-test. Taking into account both results, we, therefore, decided to proceed with a 2:1 randomisation on a total of 60 patients (40 in the TG and 20 in the CG). Low-risk-biased judgement is reached for bias arising from the randomisation process.[11]

Continuous variables are reported as means±SD. Categorical variables are reported as counts and percentages. Statistical comparisons were performed with the use of Student's t-test, paired t-test, χ^2 test or Fisher's exact test, as appropriate.

Table 1 Patient data

Parameter			
Group	**Treatment**	**Control**	**P value**
N	49	22	–
Age, mean (years)	37.6	45.3	0.005
SD	9.9	11.7	
Weight, mean (kg)	93.3	94.7	0.554
SD	8.8	9.5	
BMI, mean	34.8	34.2	0.367
SD	2.7	2.5	
Female, n	46	20	0.651
%	94	91	

BMI, body mass index; SD, standard deviation.

Estimated effects are given with their 95% CIs. All tests were two tailed and a p value of less than 0.05 was considered to be statistically significant. No imputation of the data was performed. Analyses were performed with IBM SPSS Statistics for windows, V.25 (IBM) (see also online supplemental appendix).

RESULTS

Patients

Between March 2017 and November 2018, 71 patients were included (figure 2). Mean age was significantly ($p<0.05$) higher in the TG (49 patients, 45.3 (11.7) years) than in the CG (22 patients 37.6 (9.9) years). Age-adjusted analyses found no significant differences from the unadjusted ones.

The mean BMI at baseline was similar in both groups (34.2±2.5 kg/m^2 vs 34.8±2.7 kg/m^2 in CG and TG, respectively).

After 6 months of dietary follow-up, three patients from the CG did not undergo the procedure. One patient was lost to follow-up after 3 months. One patient developed a psychiatric contraindication. The last patient had reached a BMI of 25.5 kg/m^2 after 6 months, and declined the offered endoscopic treatment. Demographic data are shown in table 1.

Procedure details

The mean procedure duration was 88 min (min 44, max 146 min). An average of 9 sutures were placed (max 12, min 5). The length of hospital stay was one night, except for one patient who stayed two nights due to a mild inhalation during extubation.

Adverse events

Fifty-four patients of the entire treated group (79.4%) reported transient abdominal cramps (mean median Visual Analogue Scale (VAS) of 5±3) for up to 3 days, transient nausea (45 patients (66.2%), VAS 4±3) or mild vomiting (45 patients, VAS 1±2.7), none of them was considered severe.

One aspiration pneumonia occurred at extubation and was procedure related. The patient was given antibiotics and was discharged per protocol after 2 days. No adverse events required readmission or surgical intervention, and no mortality occurred. No serious adverse events occurred during the study. Table 2 shows adverse events in both groups.

Table 2 Adverse events in the treatment group and in the control group

	Treatment	Control	P value
N	30	15	
Cramp, mean	5.5	5.2	NS
95% CI	(4.6 to 6.4)	(3.6 to 6.8)	
Nausea, mean	4,6	2,5	NS
95% CI	(3.6 to 5.6)	(1.0 to 4.0)	
Vomiting, mean	2,3	1,5	NS
95% CI	(1.4 to 3.3)	(0.1 to 3.0)	

CI, Confidence Interval; NS, not significant.

Weight loss outcomes and follow-up

Of 71 included patients, 68 underwent the treatment. Of these, 41 patients were available for 12-month post-treatment follow-up in the TG and 16 in the CG. At 1 year after treatment, mean median EWL and TBWL compared with baseline were 42.7% and 11.9% for the TG and 51.3% and 11.5% in the CG. During the initial 6-month comparison period, weight loss was significantly higher in the TG than in the CG (mean (95% CI) median (min–max)% EWL of 24.2 (20.8 to 27.6), 41.1 (26.7 to 55.5)), 38.5 (31.1 to 46.0) compared with 5.2% (1.3% to 9.2%), 7.70% (−1.2% to 16.6%), 13.4% (−0.7% to 27.5%) at 1, 3 and 6 months, respectively. The mean difference in EWL between the two groups was 19% (13.2–24.8, $p<0.00100.03$), 33.4% (12.1–54.7, $p<0.00100.01$) and 25.2% (11–39.4, $p<0.00100.01$) at 1, 3 and 6 months, respectively. Longer-term follow-up of the TG demonstrated a %EWL of 51.7% (24.63–78.83)) and 41.3% (31.57–51.04) at 9 and 12 months, respectively (table 3 and figure 3). Cut-off weight loss is shown in table 4.

Drinking satiety test

At baseline, mean ingested volume was 440 mL in the TG (n=43) and 374 mL in the CG (n=19) (difference between groups $p=0.174$). At 6 months, the ingested volume was 233 (200–266) mL in the TG (n=35) and 346 (254–440) mL in the CG (n=18), relating to $p<0.05$); Overall, 1 year after treatment for the 17 treated patients with available data, ingested volume dropped from 440 (387–494) ml at baseline to 208 (175–242) mL ($p<0.001$) (see online supplemental appendix table 3).

Quality of life

SF36 physical component score improved in the TG from 46.3 at baseline to 52.8 at 6 months ($p<0.01$) and 53.5 at 1 year ($p<0.001$). At 6 months, the score was also significantly higher in the TG compared with the CG (52.8 vs 45.1 $p<0.05$). The mental component score increased from 38.0 at baseline to 45.8 at 6 months ($p<0.01$) and 41.9 at 1 year ($p=0.360$). The difference between the TG and the CG at 6 months was below statistical significance (45.8 vs 39.2 $p=0.059$) (see online supplemental appendix table 2).

Other parameters

Other comorbidities were also noticed although the protocol was not designed for this purpose. Four patients had type 2 diabetes treated with oral therapy, and two still required treatment 12 months after E-ESG. Hypercholesterolaemia and hypertriglyceridaemia were observed in 30 and 33 patients at baseline vs 13 and 22 1 year after therapy. Mean transaminases level Serum Glutamo-Oxalate Transaminase (SGOT) and Serum Glutamo-Pyruvate Transaminase () dropped from 23 and 29 IU to 21 and 26 IU, respectively.

DISCUSSION

The two major messages to be taken from this randomised controlled study are that endoluminal gastric restriction using

Table 3 Weight loss outcomes over time, up to 1-year post-E-ESG in both groups (treatment performed at baseline (procedure) or after 6 months of dietary and lifestyle counselling (control))

	Baseline		3 months		6 months		12 months		18 months
	Procedure	Control	Procedure	Control	Procedure	Control	Procedure	Control	Control
N	49	22	44	22	45	21	41	16	16
Weight, mean	93.3	94. 7	84. 2	93.5	82. 9	93. 0	81. 5	83. 5	83. 9
95% CI	(90.77 to 95.85)	(90.46 to 98.92)	(81.36 to 87.03)	(88.42 to 98.51)	(79.71 to 85.99)	(87.23 to 98.70)	(78.03 to 84.90)	(76.03 to 90.87)	(75.64 to 92.10)
BMI, mean	34.8	34.2	31.6	33.7	31.2	33.4	31.0	29.7	30.1
95% CI	(34.00 to 35.53)	(33.04 to 35.26)	(30.83 to 32.41)	(32.20 to 35.22)	(30.33 to 32.06)	(31.62 to 35.14)	(29.89 to 32.02)	(27.85 to 31.58)	(27.77 to 32.35)
EWL (%), mean	–	–	34.5	7.7	38.6	13.4	42.7	43.6	51.3
95% CI			(29.12 to 39.82)	(1.16 to 16.56)	(31.11 to 45.98)	(0.74 to 27.51)	(33.14 to 52.33)	(26.87 to 60.29)	(21.89 to 80.66)
TBWL (%), mean	–	–	9.6	1.4	11.0	2.7	11.9	10.9	11.5
95% CI			(8.07 to 11.03)	(0.37 to 3.22)	(8.86 to 13.15)	(0.14 to 5.44)	(9.32 to 14.46)	(7.02 to 14.70)	(6.54 to 16.37)

The weight loss 1 year after E-ESG corresponds to 12 months values in the procedure group and 18 months values in the control group, follow-up being calculated from randomisation.
Arrows show the time of the switch to E-ESG in the control group.
BMI, body mass index ; CI, confidence interval; E-ESG, endoscopic suture gastroplasty with the endomina; EWL, excess weight loss ; TBWL, total body weight loss.

the Endomina System provides, in combination with routine moderate dietary and lifestyle counselling, sustained weight loss and QoL improvement at 1 year and, over a 6-month period, dramatically improves results over lifestyle couselling alone.

The results reported here at 1 year and for the comparison at 6 months with the CG surpassed the PIVI criteria that have been proposed for an EBT intended as a primary obesity intervention in class I/II obese individuals (25% EWL measured at 12 months, and 15% more EWL compared with a CG).[9] In our study, for ethical reasons and motivational purposes, patients in the CG were offered the procedure at 6 months. The efficacy of the treatment was further confirmed by weight loss observed after cross-over switch to therapy in the CG, who achieved similar results at 1 year compared with those patients who underwent endoscopic therapy at baseline.

It is difficult to compare our results with other endoscopic restrictive therapies because the single prospective RCT involving endoluminal suturing of the stomach was sham-controlled and performed with the POSE procedure.[3] The results of that study were not as good as those observed here but are not fully comparable with our results since our CG did not receive a sham procedure at baseline. It is possible that this had a placebo effect and reduced the observed efficacy of the procedure. These somewhat disappointing results contrasted with the outstanding weight loss observed in uncontrolled postmarketing studies. Two meta-analyses regarding ESG with the Overstitch device have reported 62%[4] and 58% EWL[12] at 12 months. These data were collected from postmarketing retrospective studies, often evaluated in cash-paying patients, conditions which are recognised to overestimate the results when compared with prospective studies where the treatment cost is borne by a source other than the patient. Regardless, these results are encouraging and preliminary reports suggest that weight loss could be maintained at 2 and 5 years. A randomised controlled study with the Overstitch is ongoing (MERIT Trial NCT03406975) and the results from this trial will likely provide insight regarding the true efficacy of this technique. A case-matched study compared high-intensity diet and lifestyle therapy (HIDLT) versus ESG with the Apollo device.[13] This study showed a greater TBWL at 12 months (20,6%) in the ESG group than in the HIDLT (14.3%). This is, however, difficult to compare with the moderate dietary and lifestyle counselling that we proposed in our study and which appears atleast in our hands, closer to routine practice.

The safety of the procedure reported here was particulary good, with no device-related SAEs observed.This is in line with safety reported for other endoluminal techniques with a low incidence of SAEs, reported to be between 1% and 2%.[4 12] In our study, very few postoperative medications were given compared with other publication.[14] Inherent to the technique, stomach cramps and nausea are easily manageable and always resolve within a few days.

Achieving an estimated 12% TBWL at 1 year in class I or II obese patients is probably not enough to justify reimbursement for all of these patients in many countries but the weight loss observed at mid-term might justify a cost–beneficial approach in patients who have associated comorbidities such as diabetes and non-alcoholic steatohepatitis. For example, a 5% wt loss improves insulin sensitivity and a 10% TBWL, which is achieved in >50% of our patients at 1 year, is usually considered as a landmark for major improvement in insulin sensitivity and lipid metabolism.[15 16] Further studies in these specific groups would be useful.

In addition, the significant improvement observed when this technique was combined with lifestyle counselling suggests that it could be offered as an initial approach to obese patients. The advantage of this type of endoluminal approach is that it is less invasive, with an extremely low risk of complications and, as

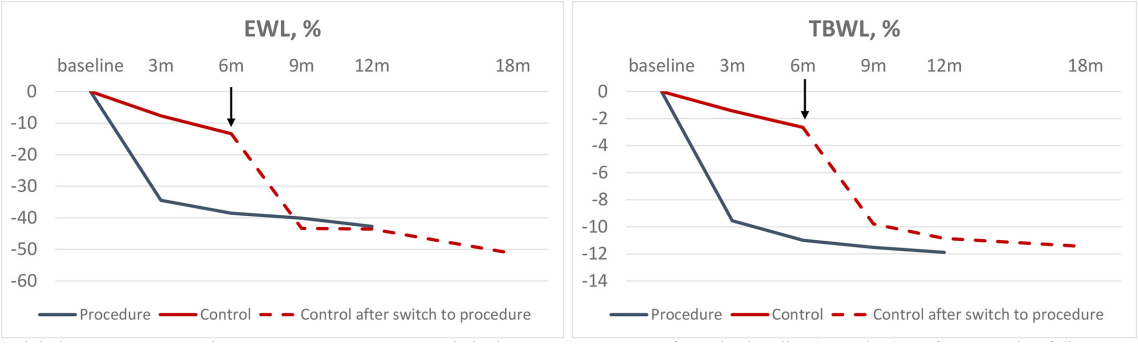

Figure 3 Weight-loss outcomes over time. E-ESG, endoscopic suture gastroplasty with the Endomina platform; EWL, endoscopic suture gastroplasty with the Endomina platform; TBWL, total body weight loss.

previously shown with other endoluminal techniques, it does not rule out further transabdominal surgical approaches if needed in the course of this chronic disease.[17] This is of particular importance since repeated transabdominal surgery is particularly difficult and associated with significantly more complications than primary surgery.

A dramatic improvement in QoL was also demonstrated at 6 months compared with the CG and at 12 months compared with baseline for the whole group. This type of improvement in SF36 QoL score had been previously shown for bariatric surgeries, and inconsistently in non-surgical weight loss programmes.[18] This is the first study to show this type of improvement in QoL after E-ESG.

From a more practical point of view, the duration of the procedure has been reduced compared with earlier studies, despite the fact that more sutures were placed. The 88 min average duration of the procedure could allow the procedure to be performed under deep sedation rather than with orotracheal intubation, and could lead to faster recovery and possible discharge on the day of the procedure. As previously shown, the need for hospitalisation is significantly less for ESG compared with laparoscopic sleeve gastrectomy or laparoscopic adjustable gastric band procedures.[14 19]

Limitations of this study include a relatively small number of patients, calculated on the basis of primary outcome fulfilment, and a potential bias in age at selection. Patients were older in the TG. Older age is, however, a negative predictive factor of weight loss after laparoscopic adjustable gastric band surgery.[20 21] In a systematic review, 7 out of 14 studies found a negative correlation between success and age and the seven others did not find any correlation.[22] When looking at correction bias for age, the %EWL between the TG and the CG at 6 months is 23.8% (95% CI 8.91% to 38.63%) (and 25.2% (95% CI 10.98% to 39.35%) without). This difference is still more than 15% and statistically significant ($p<0.001$).

Table 4 Percentage of patients achieving more of 5%–10% and 15% TBWL 1 year after the procedure (ie, 12 and 18 months after starting the study (randomisation) in treatment and control group, respectively)

	Treatment	Control
	12 months	18 months
N	41	16
>5% TBWL	75.6%	68.8%
>10% TBWL	51.2%	50.0%
>15% TBWL	34.1%	43.8%

TBWL, total body weight loss.

The population sample size was estimated using data from previous studies. Those have shown a moderate effect with 5%–10% TBWL at 1 year with intensive lifestyle management alone,[23 24] which is better than in our study (2.65% TBWL at 6 months). This is probably because our nutritional counselling was of moderate intensity in both groups, and control patients knew from the beginning that they could undergo the procedure after 6 months.

In conclusion, this study demonstrated that E-ESG in combination with lifestyle modification dramatically improves the results of lifestyle modification alone, both in terms of weight loss at 6 months after the procedure and in QoL improvement. Starting with lifestyle modification might even reinforce the efficacy of ESG. At 1 year, weight loss and other parameter improvements are maintained. Even if long-term follow-up is still mandatory, this strongly suggests that ESG with Endomina is safe and effective and could play a role in the management of obesity for selected patients.

Twitter Ivo Boskoski @ivoboskoski

Acknowledgements The authors acknowledge the contribution of medical writer, Sandy Field, PhD, for editing this manuscript, and Hassane Njimi, PhD, for his help with the statistical analysis.

Collaborators Hassane Njimi; Sandy Field

Contributors VH: writing the protocol, conducting the study, data analysis and interpretation, writing the manuscript, reviewing the manuscript IB: writing the protocol, conducting the study, writing the manuscript VB: conducting the study, data collection, critical revision of the manuscript. PVO: conducting the study, data collection and analysis, writing and critical revision of the manuscript. GC: critical revision of the manuscript. MAB: writing the protocol, conducting the study, data analysis and interpretation, writing the manuscript, critical revision of the manuscript. JD: writing the protocol, conducting the study, data analysis and interpretation, writing the manuscript, critical revision of the manuscript.

Funding This study is an academic study conducted in two centers. Endo Tools Therapeutics SA provided the instruments free of charge and a grant covering data management expenses to each center. Vincent Huberty and Jacques Deviere are shareholders of Endo Tools Therapeutics SA, which was initially a start-up of the Université Libre de Bruxelles where they are appointed.

Competing interests This study is an academic study conducted in two centers. Endo Tools Therapeutics SA provided the instruments free of charge and a grant covering data management expenses to each center. Vincent Huberty and Jacques Deviere are shareholders of Endo Tools Therapeutics SA, which was initially a start-up of the Université Libre de Bruxelles where they are appointed.

Patient consent for publication Not required.

Ethics approval The protocol was approved by the Ethics Committees at each institution.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Full anonymised database is available on request for meta-analysis or comparison trials.

ICF, protocol and SAP are available on request.The request should be asked at vincent.huberty@erasme.ulb.ac.be.

ORCID iDs
Vincent Huberty http://orcid.org/0000-0003-1995-574X
Ivo Boskoski http://orcid.org/0000-0001-8194-2670
Marc A Barthet http://orcid.org/0000-0001-6589-7160

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