Endoscopic Suturing for Transoral Outlet Reduction Increases Weight Loss After Roux-en-Y Gastric Bypass Surgery

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BACKGROUND & AIMS: Weight regain or insufficient loss after Roux-en-Y gastric bypass (RYGB) is common. This is partially attributable to dilatation of the gastrojejunostomy (GJ), which diminishes the restrictive capacity of RYGB. Endoluminal interventions for GJ reduction are being explored as alternatives to revision surgery. We performed a randomized, blinded, sham-controlled trial to evaluate weight loss after sutured transoral outlet reduction (TORe). **METHODS:** Patients with weight regain or inadequate loss after RYGB and GJ diameter greater than 2 cm were assigned randomly to groups that underwent TORe (n = 50) or a sham procedure (controls, n = 27). Intraoperative performance, safety, weight loss, and clinical outcomes were assessed. **RESULTS:** Subjects who received TORe had a significantly greater mean percentage weight loss from baseline (3.5%; 95% confidence interval, 1.8%−5.3%) than controls (0.4%; 95% confidence interval, 2.3% weight gain to 3.0% weight loss) ($P = .021$), using a last observation carried forward intent-to-treat analysis. As-treated analysis also showed greater mean percentage weight loss in the TORe group than controls (3.9% and 0.2%, respectively; $P = .014$). Weight loss or stabilization was achieved in 96% subjects receiving TORe and 78% of controls ($P = .019$). The TORe group had reduced systolic and diastolic blood pressure ($P < .001$) and a trend toward improved metabolic indices. In addition, 85% of the TORe group reported compliance with the healthy lifestyle eating program, compared with 53.8% of controls; 83% of TORe subjects said they would undergo the procedure again, and 78% said they would recommend the procedure to a friend. The groups had similar frequencies of adverse events. **CONCLUSIONS: A multicenter randomized trial provides Level I evidence that TORe reduces weight regain after RYGB. These results were achieved using a superficial suction-based device; greater levels of weight loss could be achieved with newer, full-thickness suturing devices. TORe is one approach to avoid weight regain; a longitudinal multidisciplinary approach with dietary counseling and behavioral changes are required for long-term results. ClinicalTrials.gov identifier: NCT00394212.**

Keywords: Endocinch; Overstitch; Stomaphyx; Dilated Anastomosis.

Roux-en-Y gastric bypass (RYGB) remains one of the most effective weight loss procedures, resulting in an average excess weight loss (EWL) at 1 year of approximately 70%.[1] RYGB also results in improved quality of life and reversal of major cardiovascular and metabolic risk factors, including type 2 diabetes mellitus, dyslipidemia, and other obesity-related comorbidities.[1] Although the exact mechanisms are not clear and likely are multifactorial, weight loss after RYGB is partially the result of its restrictive and malabsorptive components.

Although RYGB is highly effective, approximately 10%–20% of patients lose less than 50% at 1 year.[2] In addition, significant weight regain after gastric bypass has been reported in approximately 15%–20% of patients, but likely is higher.[3–6] Negative consequences of weight regain on the health and quality of life of the RYGB patient can be considerable. Prior research documents a significant correlation between weight regain and the incidence of type 2 diabetes mellitus recurring or worsening in patients with initial resolution of the disease. These results also have shown that poor postoperative well-being is associated with weight regain.[6–8]

Although the etiology of weight regain is not completely understood, it likely is multifactorial with interaction of a myriad of psychosocial and behavioral parameters, as well as adaptive physiologic changes that occur after bariatric surgeries, including changes in basal metabolic rate and satiety regulatory mechanisms.[6,9–11] Loss of the restrictive aspect of the RYGB owing to enlargement of the gastric

Abbreviations used in this paper: AT, as treated; CI, confidence interval; EWL, excess weight lost; GJ, gastrojejunostomy; ITT, intent-to-treat; LOCF, last observation carried forward; LS, least squares; RYGB, Roux-en-Y gastric bypass; TFEQ, Three-Factor Eating Questionnaire; TORe, transoral outlet reduction; VAS, visual analog scale.

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pouch or gastrojejunostomy, which may lead to partial loss of the satiety response, also has been implicated as a causative factor for weight regain.[12,13] Indeed, in an evaluation performed by Abu Dayyeh et al,[13] gastrojejunostomy (GJ) stoma diameter was associated significantly with weight regain after RYGB surgery in a univariate analysis and this association remained significant in a linear regression model that adjusted for several known or purported risk factors for weight regain.

Although a dilated GJ can be treated with surgical revision, the procedure requires a technically difficult surgical dissection with considerable risk of morbidity and surgical complication, which range between 15% and 50%.[14–20] Very few reports have described surgical revision for outlet reduction because the risk-to-benefit ratio of dilated GJ revision surgery generally is considered unfavorable. The advent of endoluminal approaches offer the option of substantially improving the risk/benefit relationship of revision procedures, allowing for avoidance of intra-abdominal dissection and the associated morbidity. Endoluminal suturing was first described for bariatric revision in 2004.[21] Since that time, several suturing devices, tissue plication platforms, and tissue ablation techniques have shown various degrees of efficacy in the management of weight regain after RYGB.[22–30] However, clinical information regarding endoluminal therapies primarily has been anecdotal. Therefore, evidence-based choices for treating inadequate weight loss or weight regain after RYGB with endoluminal interventions are not well defined.

In this report, we present results from the Randomized Evaluation of Endoscopic Suturing Transorally For Anastomotic Outlet Reduction (RESTORe) clinical study, a randomized, sham-controlled trial undertaken to evaluate the safety and effectiveness of an endoluminal approach (ie, transoral suturing using the Bard EndoCinch Suturing System, C.R. Bard, Inc, Murray Hill, NJ) for treating weight regain/inadequate weight loss after RYGB.

Materials and Methods

Trial Design

RESTORe was a prospective, multicenter, randomized, blinded, sham-controlled trial evaluating the effectiveness of transoral outlet reduction (TORe) in post-RYGB patients who experienced inadequate weight loss or significant weight regain. Enrolled patients were randomized to undergo TORe or sham endoscopy (controls). The study was conducted with the approval of local institutional review boards and the US Food and Drug Administration. All patients provided written informed consent. Before participating in the randomized phase of the program, study endoscopists were required to perform lead-in cases to establish the investigator's proficiency with the device and TORe technique. An independent Data Safety Monitoring Board was appointed to ensure that study participants were not exposed to unnecessary or unreasonable risks. The Data Safety Monitoring Board met periodically during the enrollment phase of the program. All authors of this study had access to the study data and had reviewed and approved the final manuscript.

Participants

Patients between ages 18 and 65 years with a body mass index between 30 and 50 kg/m^2 at least 6 months or more after RYGB with inadequate weight loss or weight regain and a GJ diameter of 2 cm or more were considered for inclusion in this study. The criterion for GJ diameter was established on the basis that during the initial RYGB the GJ generally is constructed to ultimately be less than 15 mm in diameter, and diameters of 2 cm or greater have been associated with failure to obtain or maintain appropriate weight loss.[31] Inadequate weight loss was defined as failure to achieve 50% or more EWL after surgery, and weight regain was defined as a weight gain of more than 5% EWL from nadir. Patients were excluded if any of the following criteria applied: lost 2% or more of body weight over the period of at least 3 months preceding the screening assessment; recent tobacco cessation (within 3 months) or plan to quit smoking during the study; Mallampati score of 4; active cardiorespiratory, gastrointestinal, or systemic disease, or esophagogastric conditions; intragastric fistula, gastric pouch extending beyond the cardia, dilated gastric pouch (length >6 cm and width >5 cm); pouch less than 1 cm in length or very short Roux-en-Y limb (<30 cm). Patients with severe eating disorders such as bulimia (use of purgatives/laxatives), significant mobility limitations, uncontrolled depression, active substance abuse, use of medication(s) known to cause significant weight gain (within previous 3 months) or likely to require treatment with such medication(s) during the study, use of weight loss medications, and pregnancy also were excluded.

Preprocedure Assessment and Follow-Up Evaluation

Prospective candidates were screened for eligibility during a 6-week screening period by a multidisciplinary team consisting of a bariatric surgeon and/or obesity medicine specialist, endoscopist, psychologist, and registered dietician. Screening procedures included a detailed medical history, physical examination, anthropometric measurements (weight, height, waist circumference, and blood pressure), upper-gastrointestinal series, endoscopy, clinical chemistry, nutritional, and psychological assessments. Measurements of pouch size (long and short axes) were estimated using endoscope gradations and via use of a calibrated measuring tool (Olympus Endoscopic Measuring Device; Olympus America, Inc, Center Valley, PA). Pouch length was estimated from the squamocolumnar junction to the rim of the anastomosis. GJ diameter was assessed during screening endoscopy using the calibrated measuring tool placed within and at the same plane of the proximal opening of the GJ orifice. Endoscopic images were sent to a central reading facility providing an independent and standardized review, including assessment of GJ diameter and GJ area via digital morphometric measurement analysis, using a well-validated commercial software program (Medis, QCA-CMS version 6.0, Leiden, The Netherlands). Accuracy of the measurement technique was quantified to be approximately ±10%. This approach allowed for a standardized measurement independent of variations in measuring techniques used by participating endoscopists.

Laboratory evaluation of clinical chemistries including glycemic parameters (glucose, glycosylated hemoglobin [HbA1c], insulin), serum triglycerides and cholesterol (low-density lipoprotein/high-density lipoprotein/total), and hematologic measurements were performed by a central laboratory. Patients successfully completing the screening period underwent a

baseline evaluation within 7 days before the scheduled study procedure. During the baseline evaluation anthropometric measurements were repeated and patients completed a Three-Factor Eating Questionnaire (TFEQ-18), Satiety Visual Analog Scale (VAS), Short-Form 36 Health Survey, Impact on Weight Quality of Life, and Beck's Depression Inventory. For the VAS scale, patients were requested to rank on a 10-cm visual analog scale how they felt after eating a meal. The line was provided with anchors of "not at all full" at the zero marker, and "extremely full" at the 10-cm marker. Therefore, a higher score represents sensations of increased fullness after a meal.

Clinical follow-up evaluation occurred at 2 and 6 weeks and 3 and 6 months after the procedure. Telephone contacts were performed at 1 and 18 weeks. At 6 weeks and beyond, anthropometric measurements were repeated. Body weight was measured using a calibrated digital or balance scale. Waist circumference was measured using a spring-loaded measuring tape. Comorbid disease status was documented using a longitudinal assessment tool designed for evaluating bariatric surgical populations.[32] Repeat endoscopy to evaluate GJ diameter and stitch integrity was performed at 6 weeks and 6 months. Patients were seen by a nutritionist at each study visit with administration of the TFEQ and Satiety VAS at 3 and 6 months. Laboratory testing was repeated at 3 and 6 months. Beck's Depression Inventory, Impact on Weight Quality of Life, Short-Form 36 Health Survey, and patient satisfaction questionnaires were administered at the 6-month postprocedure visit. Any undesirable clinical occurrence in a participant related to the study procedure and/or investigational device (including abnormal laboratory values) that affected/or was deemed associated with the gastrointestinal system were reported as adverse events.

Interventions

Nonsteroidal anti-inflammatory drugs were discontinued 10 days before the study procedure and were disallowed during the 6 weeks after the procedure. Patients underwent a bowel preparation with overnight fast and were admitted to the endoscopy suite on the procedure day. Both TORe and sham procedures were performed under general anesthesia to ensure proper airway management. TORe was performed as follows: a Savary Guidewire (Cook Medical, Cook Endoscopy, Winston-Salem, NC) was introduced to the jejunum and the EndoCinch esophageal overtube was advanced over the dilator and secured to the bite block. A diagnostic flexible endoscope was advanced to the proximal orifice of the GJ and the tissue around the anastomotic margins was cauterized using argon plasma coagulation to thermally ablate the mucosa, leaving a small area untouched to ensure maintenance of a patent gastric outlet. The area then was abraded with a cytology brush to expose the submucosa. A second endoscope (Olympus standard diagnostic scope) preloaded with the suturing system was advanced to the ablated area for placement of suture plications. The number of stitches required varied for each procedure based on anastomosis size; however, at least 2 stitches were placed to achieve a targeted immediate postprocedure GJ diameter of approximately 5–8 mm (Figure 1). This target includes transient procedure-related edema that will leave a somewhat larger anastomosis. For the sham procedure, an esophageal overtube was placed as detailed earlier. A diagnostic endoscope was advanced through the overtube and complete surveillance of the jejunum was performed. Sham endoscopy duration was at least 30 minutes, with an overtube dwell time of at least 20 minutes.

Patients were observed for a minimum of 1.5 hours to allow for recovery from the effects of general anesthesia and to monitor for adverse events. All patients were advised to stay on a liquid diet for approximately 2 weeks, advancing to full solids by week 6, followed by a healthy lifestyle maintenance diet similar to that required after the initial gastric bypass surgery.

Outcomes

The primary end point of this study was weight loss at 6 months measured as a percentage of baseline weight. A priori, several secondary effectiveness outcomes were identified, including a proportion of patients achieving a 10% and 20% EWL and any weight loss/weight stabilization (stabilization defined as within ±2% baseline weight). Additional analyses included improvement in obesity-related comorbidities, medical care resource use, quality of life, changes in eating habits, and effect on satiety. The safety end point was the incidence of treatment-related adverse events and incidence and severity of all adverse events experienced by the treatment and control arms during the 6-month study period.

Sample Size Calculation

The primary objective of this trial was to determine whether patients undergoing TORe experienced significantly greater weight loss than control patients at 6 months based on a 95% confidence interval. Based on a 2-group Student t test of means for unequal variance and unequal sample size (2:1 randomization ratio) with an α value of .05 and a power of 80%, the sample size required was determined to be 132 patients (88 in the TORe and 44 in the control group). A high screen failure rate led to enrollment being terminated prematurely; however, those

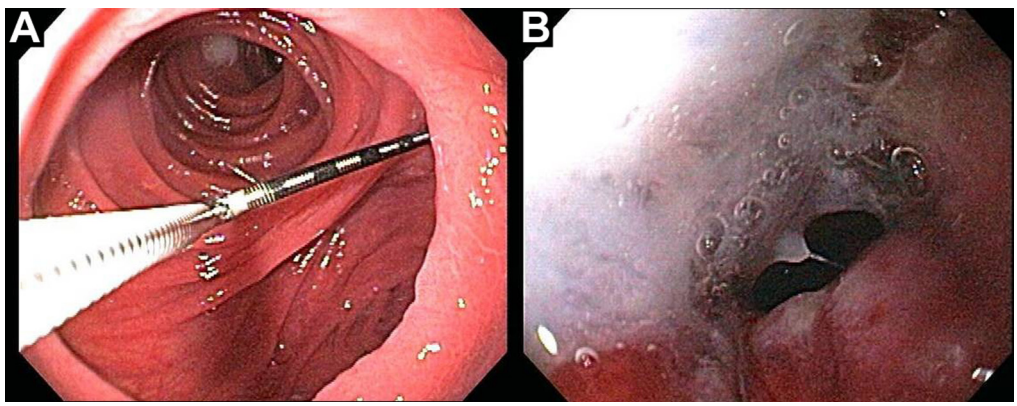

Figure 1. (*A*) Prereduction and (*B*) postreduction endoluminal images of a gastrojejunostomy.

patients enrolled the study continued to be conducted in accordance with the protocol. The investigational sites and study sponsor remained blinded to study outcomes until study completion.

Randomization and Blinding

Patients were assigned randomly to undergo either TORe or sham endoscopy, with a target ratio of 2:1. Randomization was stratified by indication for treatment (inadequate weight loss or weight regain) with permuted block randomization using a block size of 3 performed within strata. An independent contractor prepared and administered the randomization sequence, with randomization performed using an interactive voice response system. Treatment assignments were performed within 2 hours before the scheduled procedure, thus blinding the study team and endoscopist to treatment assignment before randomization. Patients were not apprised of their group assignments until the 6-month visit. Clinical follow-up evaluation was performed by research staff blinded to treatment assignment. Patients' beliefs about their treatment were collected before hospital discharge (see summary statistics for patient belief in Appendix A).

Statistical Methods

Data analyses were performed using SAS version 9.0 (SAS Institute, Inc, Cary, NC) or SPSS version 18 (IBM Corporation, Armonk, NY). Continuous variables were summarized using model-adjusted least squares (LS) means with 95% confidence intervals (CI) or medians; categoric variables were summarized with counts and percentages. The primary effectiveness end point (weight loss at 6 months) was analyzed using analysis of variance with comorbidity factors such as diabetes, dyslipidemia, and hypertension included in the model. Data sets used were the as-treated (AT) dataset (analyzed on the basis of treatment actually received and including only those patients completing the study), and the intent-to-treat (ITT) data set. Within the ITT analysis data set, patients who withdrew or became lost to follow-up evaluation had 6-month weight data imputed using a last observation carried forward (LOCF) approach.[33] Analyses of the primary end point consisted of a 2-sample Student t test (with a 2-tailed α of $<.05$ considered significant) to evaluate the overall difference in average weight loss between treatment groups. In addition, 95% CIs were calculated for the model-adjusted LS mean percentage weight loss in each treatment group and for the difference between treatment groups. Normality of the primary outcome data was explored using the SAS univariate procedure. Comparison of proportions was performed using the Fisher exact test. All reported P values are 2-sided; P values of .05 or less were considered statistically significant. Post hoc multivariate analyses (logistic and linear) using a forward stepwise procedure was performed to identify variables that made statistically significant contributions to the prediction of 6-month weight loss, expressed in absolute values and percentage changes, and achievement of milestone changes (eg, 5% absolute weight loss). Covariates included in the modeling were identified based on a review of the literature (ie, predictors of RYGB weight loss outcomes) or investigator input. Criteria for entry into the regression models at each step was a P value of 0.05 or lower, and variables were retained in the model if they maintained a P value of 0.10 or lower. To verify the assumption of randomness, an analysis was performed to compare baseline characteristics and weight loss differences (at earlier time points) between those patients with missing data and those who completed the study.

Results

The RESTORe trial was conducted at 11 bariatric centers across the United States, with 8 centers participating in the randomized phase. TORe procedures were performed between December 2006 and November 2008 by gastroenterologists and bariatric surgeons. A total of 358 potential candidates initiated the screening process and 129 were enrolled. The 2 most common exclusionary findings were GJ anastomosis less than 2 cm in diameter (32.8%) or the presence of a dilated gastric pouch (21.4%). Of 236 potential candidates who underwent screening endoscopy with GJ measurements performed by the central reading facility, 72% were diagnosed with a GJ of 2 cm or larger. Of screen failures and miscellaneous exclusions, 17 were the result of an enrollment cap initiated at the end of the study. Others were owing to various reasons including the existence of multiple exclusion criteria, not meeting all inclusion criteria based on additional examinations, failed endoscopy examinations, and principal investigator decision.

Of 129 patients deemed eligible for participation, 52 were enrolled in the lead-in phase, and 77 were enrolled in the randomized phase of the program; 50 were assigned to TORe and 27 were assigned to the control group (Supplementary Figure 1). Two patients randomized to TORe did not undergo the procedure. One patient was found to have gastric ulcers during the procedure, which were not seen during the screening endoscopy. For patient safety, the TORe procedure was not performed. The TORe procedure could not be initiated in a second patient because of a device malfunction on preprocedure testing. Despite the fact that these 2 patients did not undergo the TORe procedure and remained blinded, based on ITT principles the data from these 2 patients are included in the ITT analysis. The procedures were conducted similar to a sham and the patients remained blinded to treatment assignment, and therefore within the AT analysis they were included in the control group. An additional 6 patients were excluded from the AT analysis owing to significant protocol violations and/or for incomplete follow-up evaluation. Follow-up compliance was high, with 90% of patients completing the study. Data presented are limited to patients participating in the randomized phase of the program.

Patient Characteristics

With the exception of the prevalence of metabolic comorbidities, baseline demographics and characteristics for randomized patients were similar between the 2 groups (Table 1). Overall, the proportion of patients with metabolic-type comorbidities (eg, diabetes, dyslipidemia, and hypertension) was greater in patients assigned to TORe achieving statistical significance for diabetes and

Table 1. Baseline Patient Characteristics (ITT Population)

Parameter	TORe (n = 50)	Sham control (n = 27)	*P* value
Age, y	47.6 ± 9.46	47.6 ± 6.95	.989[a]
Sex, n (%)			
Male	3 (6.0)	1 (3.7)	1.000[b]
Female	47 (94.0)	26 (96.3)	
Ethnicity, n (%)			
Latino	3 (6.0)	1 (3.7)	1.000[b]
Not Latino	47 (94.0)	26 (96.3)	
Baseline weight, kg	101.5 ± 16.4	103.7 ± 19.6	.591[b]
BMI, kg/m^2	37.6 ± 4.9	38.6 ± 6.2	.409[b]
GJ diameter, mm	27.5 ± 6.10	29.1± 8.42	.646[c]
Pouch length, cm	4.4 ± 1.10	4.2 ± 1.18	.819[c]
Pouch width, cm	4.1 ± 0.84	4.2 ± 0.80	.772[c]
Metabolic comorbidities, %			
Diabetes	13 (26.0)	1 (3.7)	.015[a]
Dyslipidemia	16 (32.0)	5 (18.5)	.205[a]
Hypertension	19 (38.0)	4 (14.8)	.034[a]
Months from RYGB to study procedure			
Mean ± SD (n)	58.8 ± 25.7 (48)	67.5 ± 24.5 (27)	.157[b]
Minimum, median, maximum	14.9, 57.6, 121.7	31.9, 68.1, 149.3	
Weight before RYGB, kg			
Mean ± SD (n)	134.0 ± 23.9 (50)	138.4 ± 25.9 (27)	.461[b]
Minimum, median, maximum	76.1, 130.1, 220.5	95.3, 131.5, 192.8	
Maximal EWL after RYGB, %			
Mean ± SD (n)	73.2 ± 20.5 (50)	73.7 ± 21.5 (26)	.930[b]
Minimum, median, maximum	27.3, 74.6, 117.0	23.1, 75.0, 105.0	
Weight gain from nadir to baseline, kg			
Mean ± SD (n)	17.1 ± 9.7 (49)	18.1 ± 8.1 (27)	.637[b]
Minimum, median, maximum	0, 16.4, 51.5	-8.4, 19.3, 31.3	
EWL at baseline, %			
Mean ± SD (n)	47.6 ± 17.12 (50)	48.3 ± 17.5 (27)	.876[b]
Minimum, median, maximum	-7.2, 46.1, 52.5	16.3, 48.1, 82.9	

[a]*P* value from Fisher exact test.
[b]*P* value from analysis of variance with treatment as the fixed factor.
[c]*P* value from Mann–Whitney test.

hypertension. A laparoscopic approach to RYGB was used for approximately 57% of the study cohort, with a mean limb length of 112 cm. The mean duration between the original RYGB and the study procedure was approximately 5–6 years.

Procedural Characteristics

TORe was performed as desired in 98% of procedures attempted, with the 1 failure caused by a device malfunction on preprocedure testing. The median number of plications placed was 4 (range, 2–7). The mean duration of the TORe procedure (from overtube placement to withdrawal) was 107 ± 182.9 minutes. Technical success, defined as the ability to reduce the GJ to 10 mm or less, was achieved for 89.6% of cases. There were no intraprocedural adverse events reported in the randomized phase. Subjects resumed normal daily activities within a median of 3 days (range, 1–9 days) and 2 days (range, 1–5 days) for the TORe and control groups, respectively.

A blinding assessment was performed at the conclusion of the study procedure, just before discharge. The majority of patients who underwent TORe, approximately 83%, believed that they were assigned to TORe. Within the control group, responses were distributed equally, with approximately half believing they had undergone the TORe procedure and half believing they received the sham procedure.

Weight Loss Outcomes

Six-month weight loss results are presented in Table 2. Although slightly skewed to the right, there is no statistically significant evidence that the data departs from normality (Kolmogorov–Smirnov test statistic, D = 0.097198).

Because metabolic comorbidities have been shown to affect weight loss outcomes after bariatric surgery, and we had observed significantly more diabetes mellitus and hypertension subjects in the treatment group at baseline, we controlled for these factors in our analysis. By using the AT analysis, the model-adjusted LS mean percentage weight loss was significantly greater for the TORe group than for the control group (3.9 vs 0.2, respectively; lower 95% CI, 3.7; $P = .014$). By ITT analysis, using the LOCF procedure for missing data and controlling for metabolic comorbidities, the difference in weight loss similarly attained statistical significance; 3.5 vs 0.4 for the TORe and controls, respectively (lower 95% CI, 0.5; $P = .021$). There were no significant differences in weight loss

Table 2. Primary and Secondary Weight Loss Outcomes

Primary outcomes analyses: percentage weight lost from baseline				
	TORe	Sham control	Treatment difference[a]	
Analysis population	LS mean (95% CI)	LS mean (95% CI)	LS Mean (95% CI)	*P* value
ITT population: LOCF				
	3.5 (1.8–5.3)	0.4 (-2.3 to 3.0)	3.2 (0.5–5.9)	.021
ITT population: only patients completing study				
	3.8 (1.8–5.8)	0.3 (-2.8 to 3.3)	3.5 (0.6–6.5)	.020
As treated population: only patients completing study				
	3.9 (1.9–5.9)	0.2 (-2.8 to 3.2)	3.7 (0.8–6.6)	.014
Secondary outcomes analyses				
		TORe n (%)	Sham control n (%)	*P* value
Weight stabilization/weight loss at 6 months: ITT				
Achieved weight stabilization/ weight loss		48 (96.0)	21 (77.8)	.019[b]
Achieved ≥15% EWL at 6 mo		20 (41.3)	7 (25.9)	.317[b]
Achieved ≥ 20% EWL at 6 mo		15 (30.0)	4 (14.8)	.174[b]
Absolute weight loss (kg) at 6 months: ITT completers				
Mean ± SD (n)		4.5 ± 5.78 (43)	1.8 ± 5.33 (26)	.063[c]
Minimum, median, maximum		-4.4, 3.2, 25.1	-7.0, 1.3, 15.4	
Excess weight loss at 6 months: ITT completers				
Mean ± SD (n)		15.9 ± 20.90 (43)	7.7 ± 20.18 (26)	.110[c]
Minimum, median, maximum		-14.7, 10.0, 79.9	-22.4, 3.6, 71.1	

NOTE. Percentage EWL is computed as follows: ([weight at baseline - weight at 6 mo]/[weight at baseline - ideal weight at body mass index of 25]) * 100.

[a]Difference computed as LS mean for TORe group minus mean for sham control group.

[b]*P* value from 2-sided Fisher exact test comparing percentages achieved for the 2 treatments.

[c]*P* value from analysis of variance with treatment as the fixed factor.

outcomes between the patients who completed the study and those who did not, establishing that data were missing at random (data not shown in Table 2).

Both groups lost weight within the first 6 weeks after the study procedure; however, control patients showed a trend toward weight regain between the 6-week and 6-month visits; in contrast, the mean weight of the TORe group remained relatively stable between the 6-week and 6-month visit (Figure 2). Mean weight for the ITT TORe population was lower at 6 months compared with the baseline value (95.1 ± 15.22 kg vs 101.5 ± 16.41 kg, respectively; $P < .001$). This observation does not hold true for the ITT control group. In addition, the proportion of patients achieving weight stabilization or weight loss was greater for the TORe group (Table 2; 96% vs 77.8%; $P = .019$). Furthermore, the proportion of patients achieving substantial weight loss; that is, 20% EWL in the TORe group (30% vs 14.8%, respectively; $P = .174$) and the mean percentage EWL (15.9 vs 7.7, respectively; $P = 0.11$) was 2 times greater than for the controls; however, this did not achieve statistical significance. Mean weight loss calculated as a percentage of weight gained from the nadir was 23.4% ± 53.1% and 6.16% ± 28.8% for the TORe and control groups, respectively ($P = .115$).

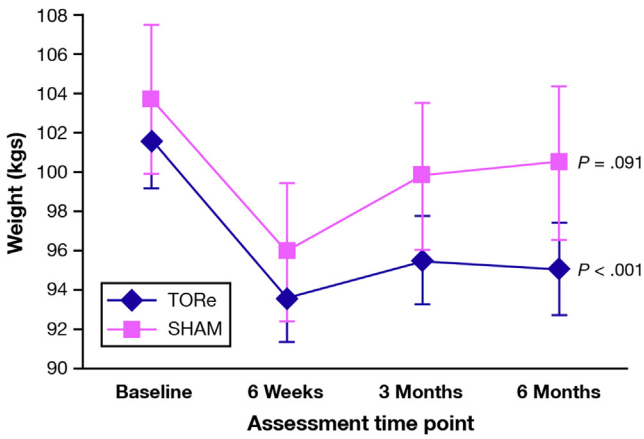

Figure 2. Weight (kg) plotted by time (mean ± standard error of the mean) (ITT population).

Results of the stepwise logistic regression modeled as a function of a dichotomous outcome (ie, achieving a 5% absolute weight loss: yes or no) or as a continuous outcome (ie, absolute weight change in kg or as a percentage), revealed that several baseline characteristics were independent predictors for 6-month weight loss (Table 3). Larger weight gains from nadir were associated positively with a 5% absolute weight loss and 10% EWL at 6 months. Increased percentage EWL at nadir was a positive predictor for achieving 20% EWL. Greater pre-RYGB weight, increased waist circumference, and later gainers (ie, nadir was achieved after first year post-RYGB) all were associated with lower weight loss outcomes at 6 months.

Post-Procedure Endoscopic Observations (TORe)

Mean GJ diameter at screening, at 6 weeks, and at 6 months postprocedure was 27.5 ± 6.1 (n = 50), 16.7 ± 6.8 (n = 41), and 20.3 ± 7.6 (n = 34), respectively. Approximately 91% and 76% of patients had one or more GJ plications that could be observed at the 6-week and 6-month endoscopic evaluations, respectively. Linear regression was

Table 3. Multivariate Analysis Results: Parameters Associated With an Increased or Decreased Likelihood of 6-Month Weight Loss

Variable	Associated parameter(s)	Parameter coefficient[a]	*P* value
Pre-RYGB weight	10% EWL	.967	.013
	% Absolute weight loss as continuous variable	.312	.006
Percentage EWL at nadir	20% EWL	1.061	.002
Weight gain from nadir	5% Absolute weight loss	1.081	.027
	10% EWL	1.065	.056
Waist circumference at baseline	15% EWL	.932	.004
	% EWL as continuous variable	.421	.000
Late gainers	15% EWL	.290	.037
	20% EWL	.107	.003
	% EWL as continuous variable	.249	.030

[a]Values greater than 1 suggest a positive correlation with weight loss, values lower than 1 suggest a negative correlation with weight loss.

performed to determine if the 6-month GJ diameter, GJ area, or percentage GJ diameter reduction were correlated with the 6-month weight loss outcomes. Although the direction of the regression line for each parameter sloped in the correct direction, these parameters were not correlated strongly with weight loss (Pearson correlation coefficients $r < |0.1|$).

Other Findings

There was a pattern toward improvement in blood pressure and lower total cholesterol, triglycerides, insulin levels, and particularly glucose values between the baseline and 6-month assessments for those patients who underwent the TORe procedure (Table 4).

More patients assigned to TORe stated they were able to comply with the healthy lifestyle eating program identified in the dietary regimen. This was most notable at the 6-month time point, at which time 85% of the patients who were assigned to the TORe group reported the ability to comply with the diet vs 53.8% of those patients assigned to the control group. In an evaluation of TFEQ change scores, the 2 groups remained essentially unchanged with respect to cognitive restraint, emotional eating, and uncontrolled eating.

With respect to the satiety VAS scores, patients assigned to the TORe group had change scores indicative of increased satiety compared with patients assigned to the control group. The mean change score (from baseline) for the TORe group at 6 months was 2.7 ± 19.2 vs -6.2 ± 26.7 ($P = .12$) for the control group.

There were no clinically significant differences between the groups in quality-of-life measures or medical care use; however, 45.3% of patients assigned to TORe indicated that they were very or mostly satisfied with their 6-month weight loss outcome vs 20% of control patients. Patient satisfaction was high regarding the procedure, with approximately 83% of patients treated with TORe indicating that they would undergo the procedure again and 78% indicating that they would recommend the procedure to a friend.

Adverse Events

There were no serious or severe device-related adverse events within the randomized phase of the program and no patient required a subsequent gastrointestinal intervention owing to a device or procedure-related complication. There was one event of a small gastric mucosal tear leading to minor bleeding that occurred within the lead-in series, which resulted from ensnarement of the EndoCinch needle with an implanted staple from the original RYGB. Within the randomized series one patient experienced pulmonary edema immediately

Table 4. Change in Variables Associated With Metabolic Risk From Baseline to 6 Months

Variable	TORe, mean ± SD (n) minimum, median, maximum (n = 50)	Sham control, mean ± SD (n) minimum, median, maximum (n = 27)	Difference[a]	95% CI of difference
Blood pressure, mm Hg				
Systolic	-6.4 ± 13.49 (42) -39.0, -3.0, 15.0	0.9 ± 12.01 (25) -23.0, 0.0, 28.0	-7.28	-13.82, -0.74
Diastolic	-5.3 ± 8.63 (42) -22.0, -5.0, 15.0	2.7 ± 10.93 (25) -18.0, 2.0, 33.0	-8.03	-12.84, -3.22
Total cholesterol, mg/dL	-4.8 ± 20.81 (40) -40.0, -7.0, 54.0	2.0 ± 19.62 (25) -46.0, 5.0, 34.0	-6.71	-17.09, 3.67
Direct LDL, mg/dL	-4.0 ± 16.50 (40) -39.0, -4.5, 28.0	0.7 ± 17.53 (25) -34.0, 0.0, 40.0	-4.65	-13.27, 3.96
HDL, mg/dL	0.7 ± 6.55 (40) -11.0, 1.0, 15.0	1.9 ± 7.90 (25) -13.0, 2.0, 16.0	-1.20	-4.82, 2.41
Triglycerides, mg/dL	-7.3 ± 30.03 (40) -88.0, -7.5, 67.0	4.4 ± 45.95 (25) -108.0, 4.0, 121.0	-11.71	-30.52, 7.09
Glucose (serum), mg/dL	-1.7 ± 7.40 (39) -19.0, -1.0, 14.0	6.1 ± 21.41 (25) -17.0, 0.0, 91.0	-7.86	-16.97, 1.24
Insulin (serum), uU/mL	-0.8 ± 3.57 (40) -11.7, -1.2, 6.0	9.0 ± 42.98 (24) -3.0, 0.5, 210.5	-9.74	-27.92, 8.44
HbA1c, %	-0.1 ± 0.37 (41) -1.0, -0.1, 0.5	-0.1 ± 0.25 (25) -0.5, -0.2, 0.4	0.04	-0.11, 0.19

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Difference was computed as the mean for the TORe group minus the mean for the sham control group.

postprocedure, which was attributed to fluid overload that required overnight observation. Overall, the proportion of patients experiencing one or more gastrointestinal adverse events at any time during the course of follow-up evaluation was slightly lower for the TORe group than for the control group (37.5% and 41.4%, respectively). For both groups, the most common events were those of nausea, vomiting, constipation, and pharyngolaryngeal pain. These events occurred primarily in the early postoperative period or were clustered around the timing of the follow-up endoscopies. A table outlining the adverse events by organ system class, and preferred terms for all randomized subjects, is included in Appendix B.

Discussion

Within the past 10 years, there has been a greater than 16-fold increase in the number of bariatric procedures performed in the United States, from 13,365 in 1998 to approximately 220,000 procedures in 2009.[34] With the number of severely obese individuals increasing, numbering nearly 15 million in the United States, the number of RYGB procedures performed will continue to increase.[34] It is very likely that we will be confronted with an increasing number of patients with inadequate weight loss or weight regain, necessitating safe and effective procedures to treat this condition. A minimally invasive approach would be preferred, and although there have been several recent reports on the use of endoluminal technologies for the treatment of weight regain after RYGB, none of the studies were designed in a manner that would allow for a treatment decision based on evidence-based principles.

The primary study end point for this trial was to assess whether weight loss at 6 months, as a percentage of the baseline weight, would be greater with TORe than with a sham control. This end point was achieved using ITT analysis with the LOCF method for missing data and controlling for metabolic comorbidities ($P = .021$), as well as for the AT analysis ($P = .014$). Of note, 2 subjects initially randomized to the treatment group who did not receive the study procedure (but received the sham and remained blinded), were analyzed as though they had undergone the treatment in the ITT analysis. The TORe procedure was not initiated in these subjects for reasons detailed earlier. In addition, 3 subjects in the ITT analysis had weights carried forward for 6 months. Along with weight loss, there was also a pattern toward lower total cholesterol, triglyceride level, insulin levels, and glucose values, and improvement in blood pressure within the TORe group. Together, these data provide positive evidence for the effectiveness and clinical benefit of the TORe procedure to reverse weight gain after RYGB.

The observed 6-month mean EWL achieved after TORe is comparable with that in a registry study evaluating the effectiveness of endoluminal restorative obesity surgery using the Incisionless Operating Platform for revision of stoma and pouch dilation (mean 6-month excess weight loss, 18%).[25] However, that study did not include a control group. For any endoluminal therapy to be considered a suitable approach to revisional bariatric surgery, the ability to perform the procedure as desired and in a safe manner with durable results is crucial. Within this trial, TORe using the EndoCinch device was performed as desired in 98% of procedures. Results from the 6-month endoscopy showed durable plications that remained in place in 76% of the patients. This is somewhat surprising considering that this suction-based device likely places sutures at a relatively superficial depth. Results may improve with a full-thickness suturing device. With respect to safety, in contrast to traditional open or laparoscopic revisional surgery with its associated risk of morbidity, the TORe procedure was very well tolerated and resulted in minimal down time and complications. The most common postprocedure events in both groups were nausea, vomiting, constipation, and pharyngolaryngeal pain. These events occurred primarily in the early postoperative period or were clustered around the timing of the follow-up endoscopies and are anticipated complications of general anesthesia and/or endoscopy.

It is possible that this study would have shown an even stronger association between TORe and weight loss had it been powered as originally intended. Still, in consideration of the safety and effectiveness results observed in this study, the risk/benefit impact of the TORe procedure is very favorable and consistent with the expectations for an endoluminal revision procedure published by the American Society of Metabolic and Bariatric Surgeons Emerging Technologies Committee in a survey of 214 bariatric surgeons.[35] The respondents indicated that a revisional endoluminal bariatric procedure that achieves 10%–20% EWL at 1 year would be considered acceptable if the risk of such a procedure was equivalent to a diagnostic or therapeutic endoscopy.

Results of the RESTORe clinical trial provide Level I evidence that establishes the safety and 6-month effectiveness of the TORe procedure for treatment of inadequate weight loss and/or weight regain after RYGB. Longer-term follow-up evaluation is needed to determine if the effect will be sustained. In addition, the procedure has high patient satisfaction. We believe that the next generation of full-thickness suturing devices likely will enhance these outcomes. Nevertheless, this is one tool in the treatment of weight regain after gastric bypass and a longitudinal multidisciplinary approach with dietary counseling and behavioral changes will be needed for enduring results.

Supplemental Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.04.002

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Reprint requests

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Conflicts of interest

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Appendix A. Summary Statistics by Belief for Treatment and Sham Groups

Table 1. Summary Statistics of the Percentage of Weight Loss From Baseline to 6 Months

Statistic	Believed treated with TORe	Believed treated with sham procedure
n	14	13
Mean	0.8	3.1
Standard deviation	3.43	6.49
Minimum	-5.6	-5.8
25th percentile	-0.7	-1.0
Median	0.4	2.2
75th percentile	3.1	7.7
Maximum	7.8	16.4

NOTE. Subjects treated with sham by their belief of what procedure they had received.
*One subject who believed treated with sham procedure had missing data at the 6-month time point.

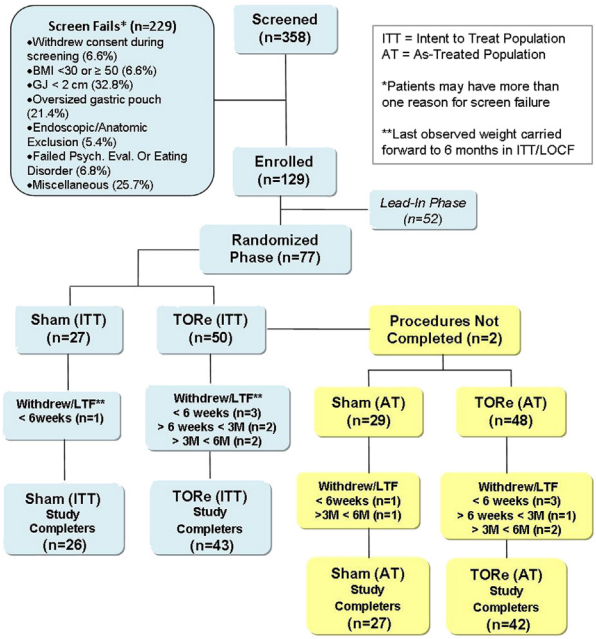
Table 2. Summary Statistics of Percentage of Weight Loss From Baseline to 6 Months

Statistic	Believed treated with TORe	Believed treated with sham procedure
n	31	8
Mean	5.2	2.5
Standard deviation	5.87	4.98
Minimum	-4.2	-1.0
25th percentile	0.8	-1.0
Median	4.2	0.1
75th percentile	9.8	5.1
Maximum	20.7	12.9

NOTE. Subjects treated with TORe only by their belief of what procedure they had received.

Appendix B. Adverse Events By SOC and Preferred Term (All Randomized Subjects)

System organ class preferred term	TORe (n = 48)	Sham control (n = 29)	Overall (N = 77)
Subjects with at least one adverse event	25 (52.1%)	19 (65.5%)	44 (57.1%)
Gastrointestinal disorders	18 (37.5%)	12 (41.4%)	30 (39.0%)
Nausea	8 (16.7%)	3 (10.3%)	11 (14.3%)
Vomiting	6 (12.5%)	4 (13.8%)	10 (13.0%)
Constipation	3 (6.3%)	4 (13.8%)	7 (9.1%)
Abdominal discomfort	4 (8.3%)	0 (0.0%)	4 (5.2%)
Abdominal pain	2 (4.2%)	1 (3.4%)	3 (3.9%)
Abdominal pain upper	1 (2.1%)	1 (3.4%)	2 (2.6%)
Diarrhea	2 (4.2%)	0 (0.0%)	2 (2.6%)
Dyspepsia	2 (4.2%)	0 (0.0%)	2 (2.6%)
Dysphagia	1 (2.1%)	1 (3.4%)	2 (2.6%)
Abdominal pain lower	0 (0.0%)	1 (3.4%)	1 (1.3%)
Gastric disorder	1 (2.1%)	0 (0.0%)	1 (1.3%)
Gastric polyps	1 (2.1%)	0 (0.0%)	1 (1.3%)
Gastric ulcer	0 (0.0%)	1 (3.4%)	1 (1.3%)
Gastritis	0 (0.0%)	1 (3.4%)	1 (1.3%)
Gingival swelling	1 (2.1%)	0 (0.0%)	1 (1.3%)
Hemorrhoids	0 (0.0%)	1 (3.4%)	1 (1.3%)
Hypoesthesia oral	1 (2.1%)	0 (0.0%)	1 (1.3%)
Adhesion-related intestinal obstruction	1 (2.1%)	0 (0.0%)	1 (1.3%)
Lip swelling	1 (2.1%)	0 (0.0%)	1 (1.3%)
Respiratory, thoracic and mediastinal disorders	7 (14.6%)	5 (17.2%)	12 (15.6%)
Pharyngolaryngeal pain	5 (10.4%)	5 (17.2%)	10 (13.0%)
Hiccups	1 (2.1%)	0 (0.0%)	1 (1.3%)
Pulmonary edema secondary to fluid overload	1 (2.1%)	0 (0.0%)	1 (1.3%)
Throat irritation	1 (2.1%)	0 (0.0%)	1 (1.3%)
Injury, poisoning and procedural complications	5 (10.4%)	2 (6.9%)	7 (9.1%)
Suture-related complication	2 (4.2%)	0 (0.0%)	2 (2.6%)
Anastomotic ulcer	0 (0.0%)	1 (3.4%)	1 (1.3%)
Postprocedural complication	0 (0.0%)	1 (3.4%)	1 (1.3%)
Postprocedural hematoma	1 (2.1%)	0 (0.0%)	1 (1.3%)
Procedural headache	1 (2.1%)	0 (0.0%)	1 (1.3%)
Procedural nausea	1 (2.1%)	0 (0.0%)	1 (1.3%)
Seroma	1 (2.1%)	0 (0.0%)	1 (1.3%)
Tooth fracture	1 (2.1%)	0 (0.0%)	1 (1.3%)
General disorders and administration site conditions	5 (10.4%)	0 (0.0%)	5 (6.5%)
Chest pain	2 (4.2%)	0 (0.0%)	2 (2.6%)
Application site erosion	1 (2.1%)	0 (0.0%)	1 (1.3%)
Fatigue	1 (2.1%)	0 (0.0%)	1 (1.3%)
Sensation of foreign body	1 (2.1%)	0 (0.0%)	1 (1.3%)
Infections and infestations	3 (6.3%)	2 (6.9%)	5 (6.5%)
Sinusitis	2 (4.2%)	0 (0.0%)	2 (2.6%)
Bronchitis	1 (2.1%)	0 (0.0%)	1 (1.3%)
Bronchitis viral	0 (0.0%)	1 (3.4%)	1 (1.3%)
Upper respiratory tract infection	0 (0.0%)	1 (3.4%)	1 (1.3%)
Nervous system disorders	3 (6.3%)	2 (6.9%)	5 (6.5%)
Headache	3 (6.3%)	1 (3.4%)	4 (5.2%)
Migraine	0 (0.0%)	1 (3.4%)	1 (1.3%)
Investigations	1 (2.1%)	2 (6.9%)	3 (3.9%)
Blood iron increased	0 (0.0%)	1 (3.4%)	1 (1.3%)
Blood pressure increased	1 (2.1%)	0 (0.0%)	1 (1.3%)
Serum ferritin decreased	0 (0.0%)	1 (3.4%)	1 (1.3%)
Cardiac disorders	1 (2.1%)	1 (3.4%)	2 (2.6%)
Bradycardia	0 (0.0%)	1 (3.4%)	1 (1.3%)
Ventricular extrasystoles	1 (2.1%)	0 (0.0%)	1 (1.3%)
Renal and urinary disorders			
Bladder discomfort	1 (2.1%)	0 (0.0%)	1 (1.3%)
Nephrolithiasis	1 (2.1%)	0 (0.0%)	1 (1.3%)
Psychiatric disorders	1 (2.1%)	0 (0.0%)	1 (1.3%)
Insomnia	1 (2.1%)	0 (0.0%)	1 (1.3%)
Surgical and medical procedures	1 (2.1%)	0 (0.0%)	1 (1.3%)
Tooth extraction	1 (2.1%)	0 (0.0%)	1 (1.3%)
Musculoskeletal and medical procedures	0 (0.0%)	1 (3.4%)	1 (1.3%)
Back pain	0 (0.0%)	1 (3.4%)	1 (1.3%)



Supplementary Figure 1. Subject disposition. BMI, body mass index; LTF, loss to follow-up; Psych. Eval., psychiatric evaluation.