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ORIGINAL CONTRIBUTIONS

Endoscopic Sleeve Gastroplasty (ESG) Is a Reproducible and Effective Endoscopic Bariatric Therapy Suitable for Widespread Clinical Adoption: a Large, International Multicenter Study

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Abstract

Objective Endoscopic sleeve gastroplasty (ESG), an incisionless endoscopic bariatric procedure, has shown impressive results in case series. This study examines the reproducibility, efficacy, and safety in three centers across two countries, and identifies key determinants for procedural success.

Design Patients who underwent ESG between February 2016 and May 2017 at one of three centers (Australia and USA) were retrospectively analyzed. All procedures were performed on an outpatient basis using the Apollo OverStitch device (Apollo Endosurgery, Austin, TX). Primary outcomes included absolute weight loss (ΔWeight, kg), change in body mass index (ΔBMI, in kg/m^2), total body weight loss (TBWL, %), excess weight loss (EWL, in %), and immediate and delayed adverse events.

Results In total, 112 consecutive patients (male 31%, age 45.1 ± 11.7 years, baseline BMI 37.9 ± 6.7 kg/m^2) underwent ESG. At 1, 3, and 6 months, Δweight was 9.0 ± 4.6 kg (TBWL 8.4 ± 4.1%), 12.9 ± 6.4 kg (TBWL 11.9 ± 4.5%), and 16.4 ± 10.7 kg (TBWL 14.9 ± 6.1%), respectively. The proportion of patients who attained greater than 10% TBWL and 25% EWL was 62.2 and 78.0% at 3 months post-ESG and 81.0 and 86.5% at 6 months post-ESG. Weight loss was similar between the three centers. Multivariable analysis showed that male sex, greater baseline body weight, and lack of prior endoscopic bariatric therapy were predictors of greater Δweight at 6 months. Three (2.7%) severe adverse events were observed.

Conclusions ESG is an effective, reproducible, and safe weight loss therapy that is suitable for widespread clinical adoption.

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Keywords Endoscopic sleeve gastroplasty · Weight loss · Obesity · Endoscopic bariatric therapy · Endoscopic suturing

Abbreviations

APC	argon plasma coagulation
EBT	endoscopic bariatric therapy
ESG	endoscopic sleeve gastroplasty
EW	excess weight
EWL	excess weight loss
ORCD	obesity-related chronic disease/condition
TBWL	total body weight loss

Introduction

The accelerating global obesity epidemic portends substantial increases in morbidity and mortality [1]. This has critical economic implications, most obviously for future healthcare spending, but also in terms of economic productivity, disability, and potential increased reliance on social safety nets. Current surgical interventions for obesity are effective, but are limited in their application and reach by poor patient acceptance and relatively high requirements for healthcare resources [2, 3]. In this context, endoluminal techniques are emerging as effective therapies in the management of overweight and obesity [4–7]. The two most widely utilized endoscopic technologies to date are intragastric balloons and the duodenojejunal liner [2, 4, 8–10]. Although used in Europe and South America, widespread dissemination has been hindered by their tolerability and safety [4]. Both techniques utilize an implanted device that remains in situ for no more than 12 months [7, 11]. These therapies, therefore, introduce the risk of device-related complications such as migration, gastrointestinal ulceration, and infection [4, 10]. Moreover, the limited duration of device implantation allows for potential weight recidivism following device retrieval, unless long-term behavioral and lifestyle changes are adopted and maintained [4]. Thus, endoscopic sleeve gastroplasty (ESG), a reportedly safe and efficacious endoscopic therapy that does not require an implanted device, has generated much interest and potentially represents a major advance in obesity therapy [7, 12–14].

Endoscopic sleeve gastroplasty is an incisionless transoral endoscopic procedure whereby a restrictive gastric luminal sleeve is fashioned within the corpus of the stomach by the application of a series of transmural sutures (Fig. 1). Using a suturing platform mounted on the endoscope (OverStitch, Apollo Endosurgery, Austin, Texas, USA), running sutures are applied along the greater curvature of the stomach, resulting in a reduction in functional volume by approximately 70%. In addition to imbrication of the greater curvature, the stomach is shortened by approximately 30% [14, 15]. Contemporary approaches spare the fundus, leaving a very small fundal pouch [16].

The Mayo Clinic in the USA first published the clinical feasibility of this technique in 2013 [13]. Two other centers (Weill Cornell Medicine, New York, NY, USA and Madrid Sanchinarro University Hospital, Madrid, Spain) adopted the procedure early in its development. The published results of their single-center series have demonstrated admirable efficacy and safety outcomes [17, 18]. Recently, the three centers combined their data of 242 patients and found a 15.2% total body weight loss (%TBWL) at 6 months post-procedure and 18.6% at 24 months [19]. However, there remains a paucity of data outside of these three centers, limiting the generalizability of the results.

Thus, we present this multicentered study as the first to report efficacy and safety of ESG for the treatment of obesity, outside the core facilities where the technique was developed, to demonstrate the generalizability of the procedure and to assess reproducibility of the results. In addition, we investigated the key determinants for weight loss outcomes.

Materials and Methods

Patients

Data from 112 consecutive patients who underwent ESG between February 2016 and May 2017 across three Western centers (Center AUS; Center US1; Center US2) were retrospectively analyzed. All patients were overweight/obese adults with no known contraindications to ESG as stated in the literature [20]. Prior to ESG, all patients were counseled on the

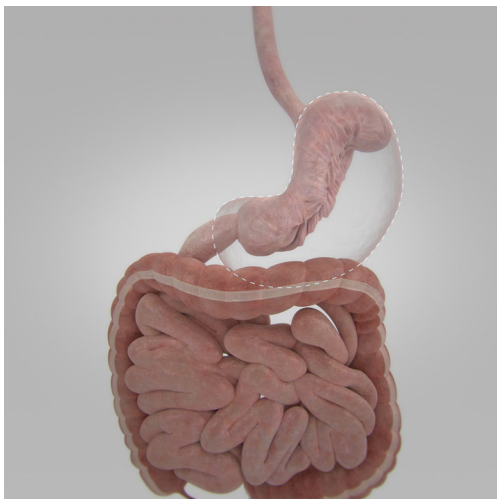

Fig. 1 Illustration of gastrointestinal tract post completed ESG procedure, with dotted lines indicating pre-ESG form. Note the small fundus that remains

spectrum of therapies available to treat obesity, including diet and lifestyle, pharmacologic treatment, endoscopic bariatric therapies (EBTs), and bariatric surgery. Informed consent was obtained from all patients. Inclusion criteria included body mass index (BMI) greater than 27 kg/m^2, and individuals with multiple unsuccessful diet and lifestyle weight management attempts. Exclusion criteria included personal or family history of gastric malignancy, active gastric ulceration, the presence of any gastric condition which required endoscopic surveillance (e.g., known gastric intestinal metaplasia), known vascular abnormalities, decompensated organ failure, obligate therapeutic anticoagulation, and pregnancy/lactation.

Procedural Technique

All ESGs were performed as described by Lopez-Nava et al. [15, 20], Sharaiha et al. [17], and Kumbhari et al. [21, 22]. All procedures were performed using general anesthesia and CO_2 insufflation and all patients were administered prophylactic antibiotics and DVT prophylaxis in line with local protocols. The patient was placed in either the left-lateral or the supine position. A diagnostic EGD was performed to confirm the absence of exclusion criteria (Fig. 2a). An esophageal overtube (Apollo Endosurgery, Austin, Texas, USA) was inserted to safeguard the esophagus and prevent decompression of the insufflated stomach. A double-channel therapeutic gastroscope (GIF-2TH180, OLYMPUS, Tokyo, Japan) was then inserted. In most instances, the medial boundaries of the proposed suture line were first marked with argon plasma coagulation (APC, Forced coagulation, Effect 2, 50 W) (VIO 300D/APC2-HF-generator; ERBE Elektromedizin, Tubingen, Germany) along the anterior and posterior walls (Fig. 2b). Using the OverStitch system, a 2/0 polypropylene suture was applied, beginning at the anterior wall at the level of the incisura angularis, with further bites taken on the greater curvature and then the posterior wall, at all times remaining lateral to the APC demarcations (Fig. 2c). The suture line was then continued in a retrograde fashion within 1 cm proximal to the initial row, from posterior wall to anterior wall, via the greater curvature (Fig. 2d). Importantly, full-thickness bites of the proximal row were staggered in relation to the distal row so as to avoid the formation of longitudinal gastric pockets (Fig. 2e). Generally, six to nine bites per suture were performed. On completion of the suture pattern, the needle was released, anchoring the leading end of the suture. Using the proprietary cinching device, the suture was pulled tight so as to bring the tissue together, and the trailing end of the suture was anchored by deploying the cinch. The suture was contemporaneously trimmed [9] (Fig. 2f).

Sutures were placed serially using this approach until within 1 cm of the gastroesophageal junction, as measured along the lesser curvature. The fundus was sutured until the endoscope began to retroflex and crossing of the suture during the stitching process occurred frequently. Therefore, only a small fundal pouch remained at the end of each procedure. Typically, a total of 6–9 sutures were used per patient. On completion of the final suture line, a check endoscopy without the OverStitch attachment was performed to ensure optimal appearance and absence of bleeding. The luminal diameter on completion of the procedure was 13–16 mm. The estimated volume of the stomach on completion of the procedure was approximately 100 mL.

Key technical elements common to all centers included using the tissue helix (Apollo Endosurgery, Austin, Texas, USA) for every bite, attaining a "pink out" with each bite to ensure a transmural bite, doubling back with each suture (using each suture to form two-rows) to ensure foreshortening of the stomach and leaving a small residual fundal pouch. The decision to perform a reinforcing inner row of sutures ("reinforcing layer") was left to the discretion of the endoscopist during the individual case.

In all three centers, patients were discharged on the same day and given daily proton pump inhibitors as well as a regimen of antiemetics, analgesics, and antispasmodics. All patients commenced a low-calorie liquid diet for at least 3 weeks, progressing through puree to a solid diet by 5 weeks post-procedure. All three centers provided patients with a comprehensive ancillary program involving intensive consultation and follow-up visits with the endoscopists and allied health professionals (dietitians, behavioral psychologists, and exercise physiologists). The programs, lasting a minimum of 12 months post-ESG, aimed to help patients establish positive dietary and lifestyle changes.

Outcomes

Patient information, including age, sex, medical history of obesity-related chronic diseases/conditions (ORCD), previous bariatric procedures, and baseline height, weight, and body mass index (BMI), was collected retrospectively from review of the electronic medical record. Patients' excess weight (EW) was calculated as the difference between their baseline weight and healthy weight (weight if their BMI was 24.9 kg/m^2) using baseline height. Primary outcomes included absolute weight loss (Δ weight, in kg), change of body mass index (ΔBMI, in kg/m^2), total body weight loss (TBWL, in %), excess weight loss (EWL, in %), and immediate and delayed adverse events and complications at 24 h, 1 week, and 1, 3, and 6 months post-procedure. The proportion of patients achieving $\geq$ 10% TBWL, $\geq$ 15% TBWL, and 25% EWL was also assessed at all time points as this has previously been recognized as a predictor of long-term weight loss maintenance and bariatric procedure efficacy thresholds [4, 19].

Data Analysis

All analyses were performed on a per protocol basis and include those subjects who reached the specified follow up time

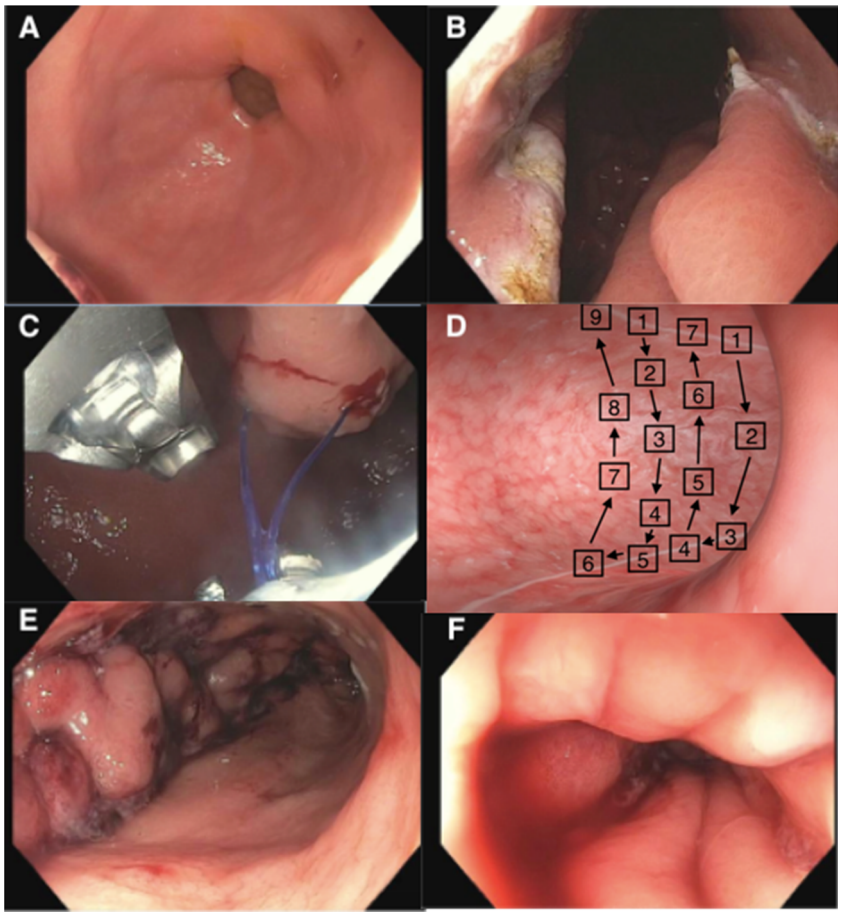

Fig. 2 Images of the gastric cavity throughout progressive stages of the ESG procedure. **a** Endoscopic view of the gastric cavity prior to ESG. **b** Markings made with APC. **c** First bite is taken. **d** Illustration of the U-shape suture pattern progressing proximally. **e** The gastric cavity in the body region immediately following completion of suturing. **f** Gastric cavity as seen from the gastroesophageal junction

points. Results are expressed as mean ± standard deviation for continuous variables and proportion (%) for categorical variables. Statistical analysis was done by means of ANOVA test for numerical variables and Chi-square analysis or Fisher's exact test for categorical variables. Multivariable regression analysis was done to compare the difference between patients of different centers, adjusting for significantly different baseline measurements. Repeat-measurement analysis was performed to track the change of weight loss outcomes. In all figures, boxplot was used to display median, minimum-maximum-range, inter-quartile-range, and outliers. Statistical analyses were performed using SPSS for Windows 22.0 software (SPSS Inc., Chicago, IL, USA). For all tests, a P value of < 0.05 was considered statistically significant.

Results

Patients

Consecutive patients ($N = 112$), who underwent ESG and reached at least 3 months follow-up, were eligible for the study. Patients' baseline BMI ranged from 28.5 to 69.0 kg/m^2. Patients undergoing ESG with Centre US1 had higher baseline BMIs and were more likely to be male in comparison to the other centers (Table 1). Ten out of 51 patients with Centre AUS had previous experience with intragastric balloon/s for weight loss, which was absent in the two US centers. Importantly, all patients experienced with intragastric balloons had either failed to respond adequately to this therapy or had suffered complete weight recidivism prior to ESG.

Efficacy

On average, total weight loss was 12.9 kg at 3 months (TBWL 11.9%; EWL 39.9%; ΔBMI 4.5 kg/m^2) and 16.4 kg at 6 months procedure (TBWL 14.9%; EWL 50.3%; ΔBMI 5.6 kg/m^2). Findings (Table 2) were similar between the three centers after adjusting for age, sex, baseline BMI, and obesity-related chronic diseases/conditions. By 3 months post-ESG, 62.2% and 35.4% of patients had TBWL greater than 10 and 15% respectively increasing to 81% and 53.8% by 6 months. The proportion of patients who attained greater than 25% EWL was 78.0% at 3 months post-ESG and 86.5% at 6 months. More than half of patients' weight loss during the follow up period was lost within the first month post-ESG (Fig. 3). However, there was no apparent weight loss plateau

Table 1 Characteristics of patients

Characteristics[a]	Total ($N = 112$)	AUS ($N = 51$)	US1 ($N = 42$)	US2 ($N = 19$)	P value[b]
Age (year)	45.1 ± 11.7	43 ± 11.9	49.2 ± 11.4	41.9 ± 9.6	ns
BMI (kg/m^2)	37.9 ± 6.7	36.7 ± 4.9	41.2 ± 8.0*	33.6 ± 4.0	< 0.001
Excess weight (kg)	36.7 ± 21.1	33.3 ± 14.9	46.5 ± 26.2*	23.9 ± 12.9	0.001
BMI category (range)					< 0.001
< 34.9	38.5	41.2	17.1	82.4[c]	
35–39.9	27.5	35.3	26.8	5.9	
40+	33.9	23.5	56.1[c]	11.8	
Sex (male)	31.3	29.4	40.5[c]	15.8	0.001
ORCD (yes)	53.6	60.8	50.0	42.1	ns
Diabetes (yes)	12.5	19.6	7.1	5.3	ns
Hypertension (yes)	23.2	17.6	28.6	26.3	ns
GERD (yes)	30.4	39.2	19.0	31.6	ns
Sleep apnea (yes)	14.3	13.7	21.4	–	ns
Previous intragastric balloon (yes)	8.9	19.6	–	–	–
Reached 6 months post-ESG (yes)	61.6	78.4[c]	57.1	26.3	< 0.001
Suture (number)	7.5 ± 2.2	6.0 ± 1.2[c]	8.9 ± 2.2	8.9 ± 1.5	< 0.001

Diabetes includes insulin resistance, pre-diabetes, and type II diabetes

ORCD obesity-related chronic disease/condition, *GERD* gastroesophageal reflux disease, *ns* not statistically significant

[a] Continuous variables in mean ± standard deviation; categorical variables in proportion (%)

[b] P values for continues variables are by ANOVA test; P values for categorical variables are by Chi-square analysis

[c] Significantly different from the other centers

observed, as all parameters continued to improve to 6 months post-ESG.

Predictors

Wide distributions of weight loss outcomes were observed. Covariates, including the treatment center, age, sex, baseline BMI, previous obesity-related chronic diseases/conditions, previous bariatric procedure history, and number of sutures used at ESG, were assessed using multi-variable linear models against weight change outcomes, adjusting for each other. Details can be found in Supplementary Table 1.

Being male was a consistent determinant of greater absolute weight loss and change of BMI at all time points, but not %TBWL or EWL. Higher baseline BMI was positively associated with absolute weight loss but negatively associated with EWL. Absence of previous experience with an intragastric balloon was a positive predictor for all weight loss parameters. Figure 4 shows the weight loss distributions at 1, 3, and 6 months post-ESG in patients in each baseline weight category. Detailed weight loss distributions in patients of differing sex and intragastric balloon history categories can be found in Supplementary Figures 1 & 2 and Supplementary Table 2.

Safety

All patients were discharged on the day of the procedure. No intraprocedural complications were encountered, across all sites. Mild adverse events such as nausea, vomiting, and abdominal pain occurred in a large proportion of patients and were anticipated. However, most notably, two severe adverse events occurred within the first week post-procedure, both of which were upper gastrointestinal bleeding. One instance was in a patient with anti-thrombin IIIa deficiency, and the decision was made to recommence low molecular weight heparin medication (LMWH) and warfarin on day 1 post-procedure. On day 4, while still on LMWH, she was found to have an INR of 2. She had hematemesis and melena with an emergent EGD demonstrating linear ulcerations in the proximal body at the suture line. The second patient had hematemesis and melena 3 days post-procedure without any inciting agents. She was admitted, managed conservatively, and discharged after 24 h.

One patient had a 3 cm perigastric fluid collection diagnosed 12 days post-procedure. Detailed explanation was described elsewhere [23]. The patient was treated with oral antibiotics and progressed well without need for drainage. No patients required conversion to surgery for the management of these complications.

Table 2 Change of weight and BMI at 1 month, 3 months, and 6 months post-ESG

Total			Unadjusted				Adjusted			
			AUS	US1	US2	*P* value[#]	AUS	US1	US2	*P* value[+]
Δ Weight (kg)	1 m	9 ± 4.6	9.3 ± 3.7	9.1 ± 4.8	8.1 ± 6.4	ns	9.6 ± 2.5	8.2 ± 2.9	9.8 ± 4.7	ns
	3 m	12.9 ± 6.4	12.5 ± 5.5	14.1 ± 8.5	12.3 ± 4.8	ns	12.9 ± 1.7	12.4 ± 2.6	13.6 ± 3.5	ns
	6 m	16.4 ± 10.7	14.2 ± 6.2	22 ± 17.3	15.3 ± 1.4	ns	15.4 ± 2.8	17.9 ± 4.5	19.6 ± 8.2	ns
	P value^	< 0.001	< 0.001	< 0.001	< 0.001					
Δ BMI (kg/m^2)	1 m	3.4 ± 3.9	3.2 ± 1.2	4.1 ± 6	2.4 ± 1.1	ns	3.1 ± 2.3	4.1 ± 2.7	2.7 ± 4.4	ns
	3 m	4.5 ± 2	4.4 ± 1.8	4.8 ± 2.6	4.3 ± 1.5	ns	4.5 ± 0.5	4.3 ± 0.9	4.7 ± 1.2	ns
	6 m	5.6 ± 3.2	5 ± 2.1	7.1 ± 5.1	5.9 ± 0.6	ns	5.3 ± 0.9	6.1 ± 1.4	7 ± 2.6	ns
	P value^	< 0.001	< 0.001	< 0.001	< 0.001					
%TBWL	1 m	8.4 ± 4.1	8.7 ± 2.7	7.8 ± 3.6	9.1 ± 8	ns	8.8 ± 2.5	7.5 ± 2.9	9.4 ± 4.7	ns
	3 m	11.9 ± 4.5	11.9 ± 4.5	11.6 ± 5.1	12.4 ± 3.3	ns	12 ± 1.3	11.4 ± 2.1	12.5 ± 2.8	ns
	6 m	14.9 ± 6.1	14 ± 5.6	16.3 ± 7.9	17.7 ± 1.7	ns	14.7 ± 2.1	15.2 ± 3.5	18.3 ± 6.3	ns
	P value^	< 0.001	< 0.001	< 0.001	< 0.001					
%EWL	1 m	28.2 ± 18.3	29.4 ± 10.8	22.8 ± 12.2	39.2 ± 38.7	0.015	28.6 ± 5.1	25.5 ± 6	34.3 ± 9.8	ns
	3 m	39.9 ± 17.3	40.4 ± 17	34.2 ± 18.3	49.4 ± 13.1	ns	38.8 ± 4.2	40.5 ± 6.6	44.1 ± 8.9	ns
	6 m	50.3 ± 22.4	49.2 ± 23.2	46.9 ± 20.3	72.1 ± 9.7	ns	48.5 ± 7.3	51.1 ± 12	65.2 ± 21.7	ns
	P value^	< 0.001	< 0.001	< 0.001	< 0.001					
TBWL ≥ 10% (%)[a]	1 m	25.8	29.5	22.2	23.1					
	3 m	62.2	61.2	59.1	72.7					
	6 m	80.8	79.4	78.6	100.0					
TBWL ≥ 15% (%)[b]	1 m	5.6	4.5	5.6	7.7					
	3 m	35.4	34.7	36.4	36.4					
	6 m	53.8	44.1	64.3	36.4					
EWL > 25% (%)[c]	1 m	52.7	65.9	36.1	53.8					
	3 m	78.0	77.6	68.2	100.0					
	6 m	86.5	85.3	85.7	100.0					

Data available: 1 month $N = 93$; 3 months $N = 82$; 6 months $N = 52$

Δ Weight change of weight from pre-procedure, *Δ BMI* change of BMI from pre-procedure, *%TBWL* total body weight loss (%), *%EWL* excess weight loss (%), *ns* not statistically significant

^ Repeat-measurement analysis, # ANOVA tests, + linear multivariable analysis adjusted by age, gender, initial BMI, and diagnosed obesity-related chronic disease/condition

[a] TBWL ≥ 10%: prevalence of total body weight loss more than 10%, as long-term weight loss outcome predictor demonstrated by literature [19]

[b] TBWL ≥ 15%: prevalence of total body weight loss more than 15%, as weight loss efficacy threshold demonstrated by ASGE Bariatric Endoscopy Tast Force [4]

[c] EWL > 25%: prevalence of excess weight loss more than 25%, as weight loss efficacy threshold demonstrated by ASGE Bariatric Endoscopy Task Force [4]

Discussion

This international multicenter study of 112 consecutive patients who underwent endoscopic sleeve gastroplasty for treatment of obesity demonstrates consistent efficacy and safety of the procedure across the study centers, and is furthermore consistent with reported outcomes in the published literature. Thus, ESG is a safe and effective endoscopic bariatric procedure with generalizability and reproducibility.

The incidence of obesity, which is recognized by the World Health Organization as a disease, has nearly doubled since 1980, and obesity-related comorbidities have become a major threat to human health [1]. Therefore, effective and readily available endoscopic procedures such as ESG, offering a viable, minimally invasive approach and clinically meaningful weight loss, has the potential to bridge the gap between conservative dietary and lifestyle counseling and highly restrictive and resource-intensive surgical procedures.

As the first study summarizing weight loss outcomes of ESG outside of the core facilities that pioneered the procedure, we report comparable and consistent findings of approximately 15% TBWL and 50% EWL at 6 months post-procedure. In

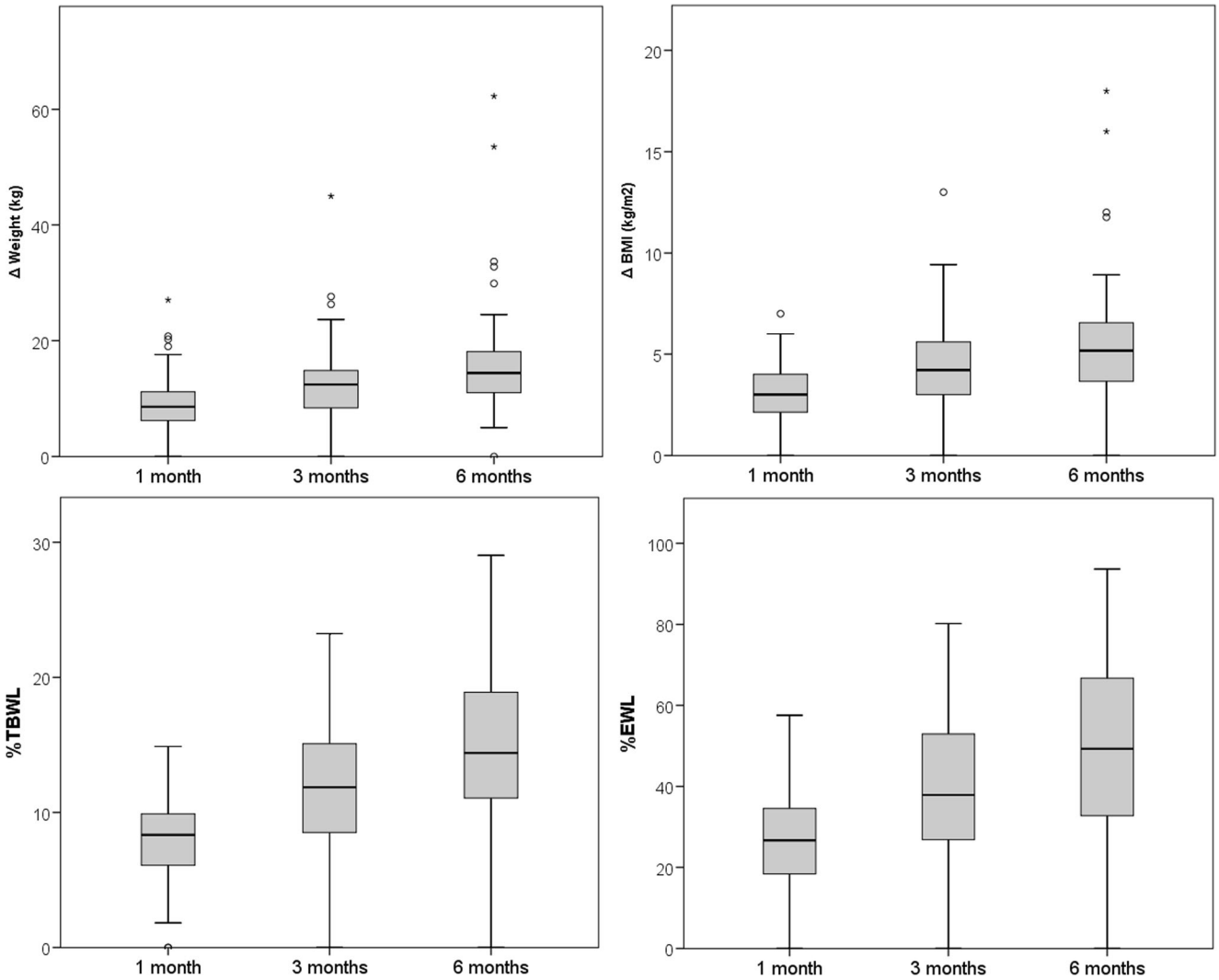

Fig. 3 Graphical depictions of **a** ΔWeight, **b** ΔBMI, **c** %TBWL, and **d** %EWL at 1, 3, and 6 months post-ESG. Figures included all data points. Outliers are defined as data points that are located 1.5 times outside the interquartile range. Asterisk indicates an outlier, degree sign indicates two outliers, and bullet indicates three outliers

a multicenter study enrolling 248 patients at the 3 pioneering centers, ESG was associated with 15% TBWL at 6 months [19].

Lopez-Nava et al. were able to demonstrate that weight loss at 6 months was highly predictive of further weight loss and long-term weight maintenance. Reaching a TBWL ≥ 10% was shown to predict weight maintenance up to 2 years post-procedure [15]. We found that approximately 60% of patients had greater than 10% TBWL at 3 months post-ESG and 80% at 6 months. Since we have demonstrated similar short-term efficacy as equivalent term results published in longer-term studies, we anticipate long-term results in our patients will be favorable.

Our findings suggest that ESG may offer superior efficacy and reduced risk of major adverse events compared to other endoscopic bariatric therapies. Minor adverse events such as nausea, vomiting, and abdominal pain were anticipated in ESG patients, thus, pharmaceutical prophylaxis was provided to all. Such minor adverse events are expected in patients undergoing endoscopic bariatric therapies, particularly those where the target site is the stomach [11, 24–26]. When comparing the efficacy of ESG to systematic reviews and meta-analyses of the most commonly utilized endoscopic bariatric therapy (intragastric balloons), ESG outcomes appear superior. For example, %TBWL appears lower with intragastric balloons at 12% (EWL 25.4%) at 6 months follow-up [11, 24–26]. Most notably, intragastric balloons have adverse events that persist beyond the first 3–5 days such as gastroesophageal reflux disease (GERD) (18.3%) as well as high intolerance rates (often around 10%) requiring premature removal of the device [26, 27]. Furthermore, more serious complications of IGB therapy include gastric ulceration, balloon deflation and potential migration, pancreatitis, and rarely,

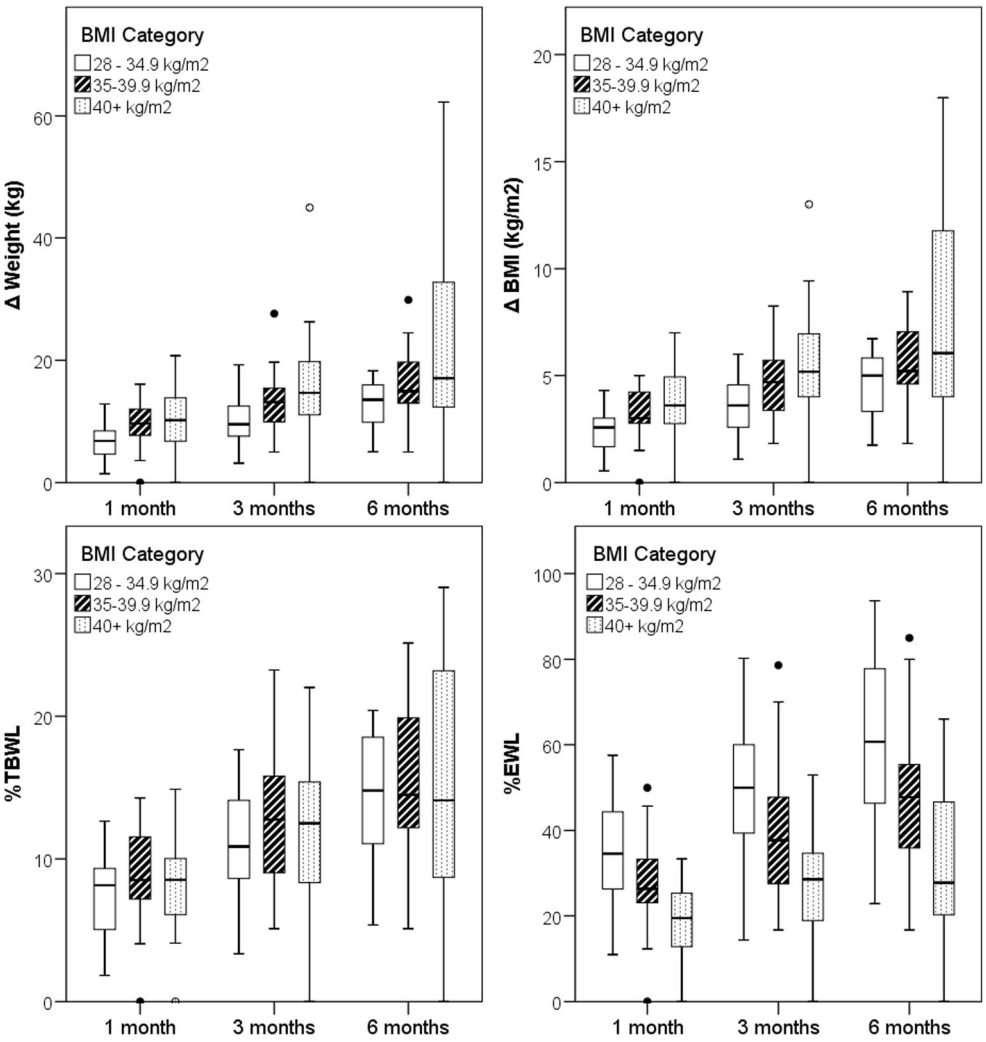

Fig. 4 Graphical depictions of **a** ΔWeight, **b** ΔBMI, **c** %TBWL, and **d** %EWL at 1, 3, and 6 months post-ESG, categorized by baseline BMI category. Figures included all data points. Outliers are defined as data points that are located 1.5 times outside the interquartile range. Asterisk indicates an outlier, degree sign indicates two outliers, and bullet indicates three outliers

gastric perforation. Persistent mild adverse events and intolerance have not been reported with ESG and were not seen in our patient cohort. Of note, the most serious adverse event in our series was in a known high-risk patient. The high level of safety in our patients post-ESG requires further study and characterization, particularly in comparison to existing EBTs.

For an EBT to have a meaningful impact on obesity, it should reach a certain threshold of efficacy that is balanced against the risks of the intervention. The Preservation and Incorporation of Valuable endoscopic Innovation (PIVI) thresholds to assess EBTs, set jointly by the ASGE and the ASMBS, recommend efficacy targets of > 25% EWL at 12 months, and a safety threshold of < 5% risk of major complication [4, 28]. ESG, as assessed in this study and as previously reported, meets these thresholds comfortably.

In addition, we acknowledge the wide distribution of weight loss outcomes reported in our study, which might indicate highly individual responses to treatment, or perhaps the existence of specific subpopulations, or phenotypes, of patients that affect the weight loss response to ESG. It should be noted, however, that these cohorts include the first cases performed at each center, and as such the presence of a learning curve may further contribute to the wide range of outcomes, particularly at the 6-month time point [14, 21]. Our multivariable analysis showed that males achieved better absolute body weight loss than females, after adjusting for baseline body size, age, medical history, and for those that previously underwent intragastric balloon therapy, type of balloon. Since the proportion of males in bariatric settings has traditionally been low worldwide [2], we suggest the possible effect of gender difference has been overlooked. More investigation into anthropometric differences (e.g., fat-free mass vs. fat mass), behavior patterns, and biopsychosocial differences is required to better predict outcomes.

Patients experienced with intragastric balloon/s for weight loss reported significantly less weight loss than those naïve to endoscopic bariatric procedures. Multiple potential factors may explain this observation, including selection bias of a relatively treatment-refractory group. Also, changes in gastric

wall thickness following intragastric balloon therapy may also lead to altered efficacy and/or durability of ESG. Furthermore, given that both intragastric balloon therapy and ESG induce gastric restriction and delayed gastric emptying, it is possible that this cohort represents a "phenotype" that is not responsive to bariatric modalities employing this combination of physiologic manipulation. However, there is an absence of evidence examining the consequences of specific bariatric endoscopic procedures (e.g., intragastric balloons) on concurrent or consecutive weight loss interventions of any form. To our knowledge, this is the first study reporting weight loss outcomes in patients that underwent more than one type of endoscopic bariatric procedure. Given that EBTs are likely to become much more widespread due to the current obesity epidemic, we predict more patients will undergo multiple EBT procedures for intensive weight loss or to address weight recidivism. We highlight here the urgent need to study the implications of various EBTs for future weight loss attempts in order to identify optimal combinations and/or permutations for specific patient subsets, or "phenotypes."

It is worth noting that patients' baseline body size was associated with different weight loss outcomes, after adjusting for all the other covariates. At 6 months post-procedure, although observed to attain a much greater absolute weight loss, patients with higher baseline BMI were not as close to their ideal weight range as those with lower initial BMI; a finding that has also been observed in the surgical literature [29, 30]. The findings have critical clinical implications. In the first instance, these observations would suggest that early intervention is key in optimizing the chances of normalizing weight. Furthermore, we suggest health professionals practicing this technique, and arguably those working with bariatric patients generally, discuss weight loss outcomes with patients from the outset to set realistic goals and manage expectations surrounding the magnitude of weight loss and the timeline to such targets. Further research is required to examine the potential for differential impacts on health outcomes following ESG, in addition to weight loss, between patients of different baseline BMI categories.

Limitations of our study include its retrospective nature, the limited long-term follow-up, and the small subset of patients with previous gastric balloon experience, which could potentially lead to type II error. While our study was strengthened by the multi-center design, there was no control group or randomization. Since previous literature indicated the relative infrequency of adverse events associated with the procedure, we felt that a multicenter study would at least allow for detection of even infrequent adverse events, if they so occurred. The loss to follow-up rate was comparable to other previous investigations of bariatric procedures [2, 16, 19]. The current study addresses proof of concept, generalizability, and safety of ESG. Randomized controlled studies with longer-term follow-up are needed.

Despite encouraging short-term weight loss and safety results, ESG's role in weight management remains unclear. To sum up, there have been no published studies directly comparing ESG to other bariatric procedures in terms of efficacy, safety, or cost. Furthermore, to our knowledge, there has been only one study assessing the changes in metabolic risk profile following ESG [17]. Future research priorities should focus on assessing the health outcomes following ESG, establishing its cost effectiveness, and examining its performance against conventional bariatric interventions, including lifestyle therapies, in a randomized fashion. In addition, predictors of procedural success and optimization of after-care all require further exploration.

Considering the significant weight loss observed, reproducibility of the results among independent centers, absence of intraprocedural events, and low prevalence of major adverse events and complications, ESG appears to be a feasible, effective, and safe treatment for obesity. The procedure, in its current form, is thus suitable for incorporation into clinical practice.

Authors' Contributions AS and VK had the concept of the work. AS, VK, and ZS completed data analysis and interpretation. All the authors had equal contributions in data collection, drafting the article, and critical revision of the article. All authors approved the final version of the article for publication.

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Compliance with Ethical Standards

Conflicts of Interest AS, EW, and VK are consultants with Apollo Endosurgery. AS and GM are consultants for BARONova. VK is also a consultant for Boston Scientific, Reshape Medical, and Medtronic. MAK is a consultant for Boston Scientific and Olympus America. ANK is a founding member, equity holder, and consultant for Apollo Endosurgery. EW is a consultant for Gore, Intuitive, Ethicon, Olympus, and EndoGastric Solutions. The remaining authors disclose no conflict of interest.

Ethics Statement All procedures performed in the study were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective study, formal consent is not required.

Consent Statement Informed consent was obtained from all individual participants included in the study.

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