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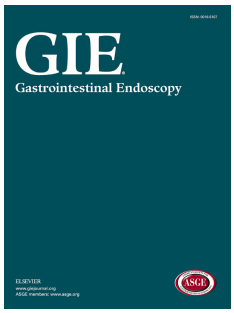

EFFECTS OF DIFFERENT TECHNIQUES OF ENDOSCOPIC GASTROPLASTY ON WEIGHT LOSS AMONG PATIENTS WITH OBESITY: A RANDOMIZED, SINGLE-CENTER PRAGMATIC TRIAL

Salvatore F. Vadalà di Prampero, MD, PhD, FASGE, Marco Geraci, PhD, Valentina Cosseddu, MSc, Chiara Rocchi, MD, Paola Bazzu, MSc, Ilaria Simonelli, MD, Marcello Fiorani, MD, Jessica Formichetti, MSc, Gabriella Manzoni, MD, Federica Di Maio, MD, Marco Massidda, MD, Simona Masia, MSc, Mariangela Puci, PhD, Giovanni Sotgiu, MD, PhD, Valentina Milano, MD, Maria A. Mancini, MD, Pierluigi M. Rinaldi, MD, Piero Giustacchini, MD, PhD, Guido Costamagna, MD, FACG, Milutin Bulajic, MD, PhD, FASGE, FACG

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1 Digestive Endoscopy Unit, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy
2 Gastroenterology and GI Endoscopy Unit, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy
3 Department of Statistics, La Sapienza University, Rome, Italy
4 Department of Nutrition, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy
5 Department of Psychology, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy
6 Department of Biostatistics, Clinical Research Centre, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy
7 Department of Radiology, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy
8 Department of Internal Medicine, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy
9 Department of Medical, Surgical and Experimental Sciences, Clinical Epidemiology and Medical Statistics Unit, University of Sassari, Sassari, Italy
10 Endocrine and Metabolic Surgery Unit, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy
11 Division of Endocrine and Metabolic Surgery, Fondazione Policlinico A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

CORRESPONDING AUTHOR

Marcello Fiorani, MD

Ospedale Isola Tiberina - Gemelli Isola

Via di Ponte Quattro capi, 39 - 00186 Rome (RM)

Ph: +39 06 68371

Fax: +39 06 68371

Email: marcellofiorani94@gmail.com

Contributors: SF Vadala Di Prampero designed the study, collected and interpreted the data, reviewed and edited the manuscript.
Geraci M, Cosseddu V, Rocchi C, Bazzu P, Simonelli I, Fiorani M, Formichetti J, Manzoni G, Di Maio F, Massidda M, Masia S, Puci M, Sotgiu G, Milano V, Mancini M.A, Rinaldi P.M, Giustacchini P, collected and interpreted the data. G. Costamagna and M. Bulajic reviewed and edited the manuscript.
SF Vadala Di Prampero, M. Fiorani, M. Bulajic, were major contributors in writing the manuscript, and all authors approved the final manuscript.

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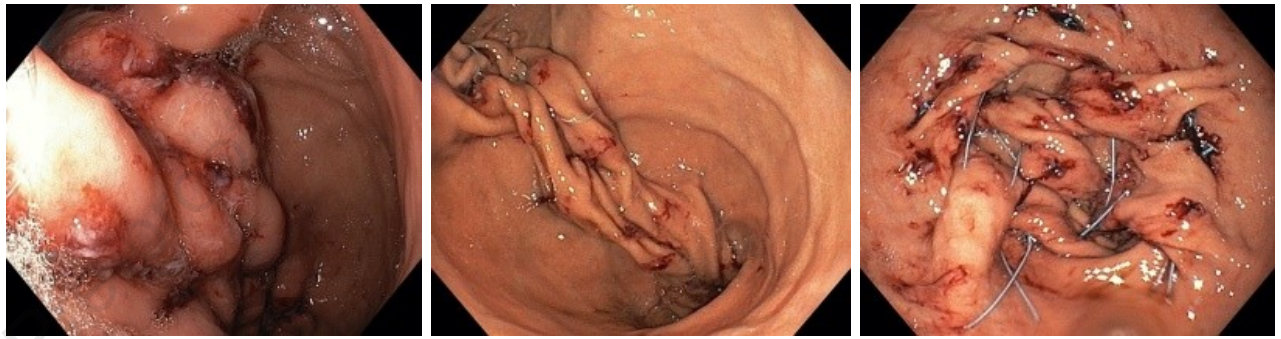
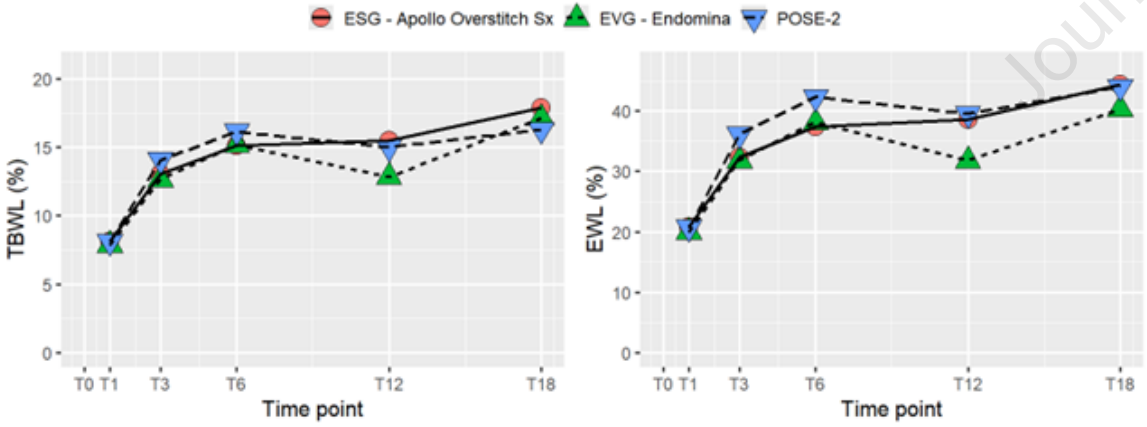
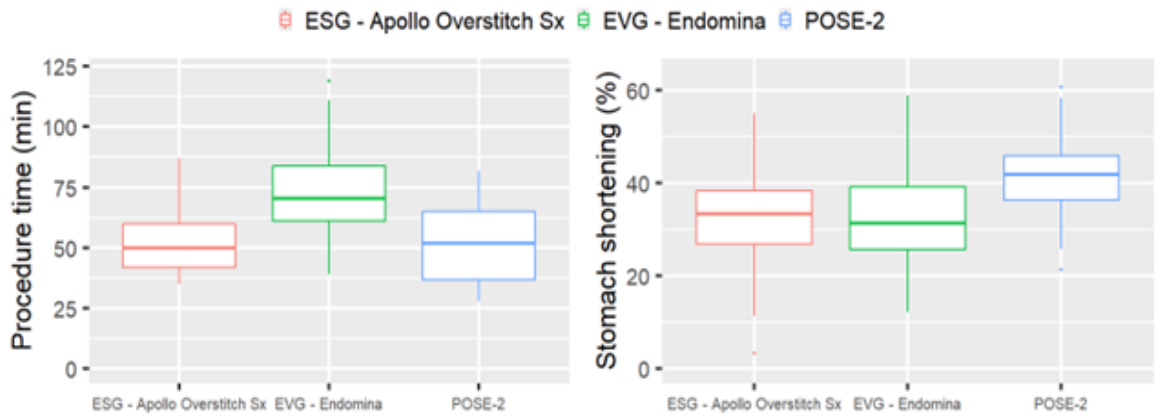
- 184 patients underwent endoscopic gastroplasty.
- The technical success rate was 100%. The serious adverse event rate was 1.1%
- ESG, EVG, and POSE-2 were equally effective, safe, and feasible interventions for managing obesity at a medium-term follow-up, with some differences in technical outcomes







ESG: Endoscopic Sleeve Gastroplasty. EVG: Endoscopic Vertical Gastroplasty. POSE-2: Primary Obesity Surgical Endoluminal-2. TBWL: Total body weight loss. EWL: Excess weight loss.

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1 Digestive Endoscopy Unit, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy

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3 Department of Statistics, La Sapienza University, Rome, Italy

4 Department of Nutrition, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy

5 Department of Psychology, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy

6 Department of Biostatistics, Clinical Research Centre, Ospedale Isola Tiberina - Gemelli Isola, Rome, Italy

7 Department of Radiology, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy

8 Department of Internal Medicine, Mater Olbia Hospital, Qatar Foundation Endowment & Gemelli Foundation, Olbia, Italy

9 Department of Medical, Surgical and Experimental Sciences, Clinical Epidemiology and Medical Statistics Unit, University of Sassari, Sassari, Italy

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11 Division of Endocrine and Metabolic Surgery, Fondazione Policlinico A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

CORRESPONDING AUTHOR

Marcello Fiorani, MD

Ospedale Isola Tiberina - Gemelli Isola

Via di Ponte Quattro capi, 39 - 00186 Rome (RM)

Ph: +39 06 68371

Fax: +39 06 68371

Email: marcellofiorani94@gmail.com

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ABSTRACT

Background and aims:
Obesity is a global pandemic requiring effective interventions. Endoscopic bariatric therapies (EBTs) are minimally invasive alternatives to surgery. We compared three techniques of Endoscopic Gastroplasty (EG): endoscopic sleeve gastroplasty (ESG) (Apollo Overstitch Sx; Boston Scientific), endoluminal vertical gastroplasty (EVG) (Endomina; EndoTools Therapeutics), and primary obesity surgery endoluminal-2 (POSE-2) (Incisionless Operating Platform; USGI Medical).
Methods: This was a single-center, randomized pragmatic study (ClinicalTrials.gov NCT04854317) involving patients who underwent EG through ESG or EVG or POSE-2. The primary endpoint was the percentage of total body weight loss (TBWL), with secondary endpoints assessing excess weight loss (EWL), safety, feasibility, anthropometric changes, metabolic and quality of life improvements.
Results: Between April 2021 and May 2023, 184 obese patients (body mass index 36.5 ± 3.0 kg/m^2) underwent EG. Follow-up rates were 56% at 6 months, 32% at 12 months, and 15% at 18 months. At 6, 12 and 18 months, patients experienced, respectively, 15.5% ± 6.0%, 14.5% ± 8.5% and 17.1% ± 10.2% TBWL and 39.3% ± 15.5%, 36.7% ± 21.4%, and 43.0% ± 26.6% EWL, with no statistically significant differences among the three techniques for both parameters ($p \geq 0.36$). The technical success rate was 100%. The serious adverse event rate was 1.1%. Anthropometric measurements, body composition, fatty liver disease and hyperlipidemia improved at 6, 12 and 18-month follow-up, as well as the quality of life measured by Baros and TSD-OC test ($p < 0.01$).
Conclusions: This study underscores the potential of EG through ESG, EVG, and POSE-2 as equally effective, safe, and feasible interventions for managing obesity at a medium-term follow-up. Results were consistent despite incomplete follow-up, the main study limitation, assuming data were missing at random.

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INTRODUCTION

The last WHO survey reports that more than 1.9 billion adults are overweight and, of these, over 650 million are obese(1). These data clearly show that nowadays obesity is a pandemic disease(2), which leads to many other health issues, and whose prevalence continues to increase worldwide(3,4).
Obesity and its related diseases are largely preventable through supportive environments that encourage healthier food choices and regular physical activity(1). However, in obese patients it's mandatory to adopt strategies to promote weight loss and prevent the development of weight-related complications(5).
When primary and secondary prevention fail, other treatment options need to be attempted, such as medical therapies, endoscopic or surgical bariatric procedures. According to the patient's body mass index (BMI) and comorbidities, a single approach or a combination of these three strategies, together with diet and lifestyle modifications, can be carried out to treat weight-related complications and prevent disease progression(5).
Concerning the endoscopic bariatric therapy (EBT), historically it was performed mainly by placement of an intragastric balloon(6), which is a mini-invasive technique that aims to induce satiety and satiation by occupying part of the stomach with a balloon made of different materials that remains in place for 6 to 12 months(7). Although the intragastric balloon is effective in causing a meaningful weight loss, some studies have reported that the results are short-lasting, with most patients regaining weight following its removal(8).
To avoid this issue, other EBTs with different profiles of safety and efficacy have been tried in this last decade; some of them have been withdrawn from the market, some others are still under scientific debate, waiting for solid literature(7).
Endoscopic Gastroplasty (EG) is an innovative EBT focusing on gastric body remodeling to treat obese patients, mostly with I and II grade of obesity. This technique aims to reduce the gastric body in a mini-invasive way, just using the endoscope and an attached suturing or plication device(7).
Nowadays three different techniques of EG are mainly described in the clinical practice: endoscopic sleeve gastroplasty (ESG) with an overstitch endoscopic suturing device (Overstitch; Boston Scientific, Marlborough, MA, USA), endoluminal vertical gastroplasty (EVG) with a simple triangulation platform and endoluminal suturing device (Endomina; Endo Tools SA [ETT], Gosselies, Belgium), and distal primary obesity surgery endoluminal (POSE-2) with an endoscopic plication system (Incisionless Operating Platform; USGI Medical, San Clemente, CA, USA).
Here we report the results at 6, 12 and 18 months of a single-center, randomized pragmatic trial evaluating the efficacy, feasibility and safety of these three techniques of EG in obese patients.

METHODS

Patients

From April 2021, through May 2023, we enrolled 203 patients at Mater Olbia Hospital's Obesity and Metabolic Diseases Department, in Olbia, Italy.
Inclusion criteria were the following: age range between 18 to 65 years; Body Mass Index (BMI) between 30-34.99 kg/m2 with previous failed nutritional attempts and with obesity-related diseases, a BMI of 35-39.99 kg/m2 with previous failed nutritional attempts and with or without obesity-related diseases, a BMI of 40-44.99 kg/m2 with previous failed nutritional attempts and with or without obesity-related diseases not fitting for conventional surgery.

Exclusion criteria were allergies or other contraindications or intolerance to the study interventions, previous surgical or endoscopic bariatric attempts, pregnancy, or child-bearing potential without contraception, life threatening conditions, unconscious or unable to express any consent.
The study protocol (240/2020/CE) was reviewed and approved by the local ethics committee on June 16th, 2020 and was conducted in agreement with national guidelines and the provisions of the Helsinki Declaration, as revised in 2000. All patients provided written informed consent to participate in the study, and additional written informed consent was obtained before any endoscopic procedure. The study protocol is available on ClinicalTrials.gov NCT04854317.

Randomization

The consecutive patients were included in one of three study groups - ESG, EVG, POSE-2 - by simple randomization in a 1:1:1 ratio with the use of a computerized system for generating random numbers(9). The operators and physicians were aware of the patient's study arm assignment, whereas the patients were not.

Trial procedures

Endoscopic gastroplasty

Patients assigned to undergo either ESG or EVL or POSE-2 were evaluated by a multidisciplinary team (including a gastroenterologist, a dietitian, and a psychologist) at baseline (T0) and at 1, 3, 6, 12 and 18 months (T1, T3, T6, T12, T18, respectively) after the endoscopic procedures.
Two experienced endoscopists in EG, as required by European Society of Gastrointestinal Endoscopy position statement(10), conducted the interventions in a quasi-randomized manner (2 procedures/day, first always by same operator) with anesthesiologist support for monitoring and general anesthesia. (A detailed description of the endoscopic procedures is provided in the Supplementary Appendix).
Patients were maintained on a full liquid diet for 3-5 days after the procedure, on semi-liquid diet for the next 3 weeks, starting a solid low-calorie diet a month later.
Daily multivitamin and mineral supplementation were prescribed for the first two months.
Right after the procedure and for the first 24 hours patients were prescribed intravenous proton pump inhibitors, analgesics and antiemetics as per our standard protocol (A detailed description of post-operative medication protocol is provided in the Supplementary Appendix).

Laboratory analysis

Levels of plasma cholesterol, triglycerides, fasting plasma glucose and glycated hemoglobin together with blood pressure were checked out before the procedure and at T1, T3, T6, T12 and T18.

Nutritional tests

Anthropometric data (height, weight, body circumferences of arm, waist, hip and calf) and body composition (fat mass, free-fat mass, body cell mass) to calculate Body Mass Index (BMI) and Waist/Hips ratio (WHR) were collected before the procedure and at the follow-up visits at T1, T3, T6, T12 and T18.

Radiological tests

A liver ultrasound with shear wave elastography was performed before and 3 months after the procedure to evaluate the degree of steatosis. A transit study examination and a barium x-ray were performed before the procedure and after 3 months to test the variation of gastric motility.

Psychological tests

Patients' quality of life (QoL) based on a combination of generic and specific instruments (TSD-OC)(11), collateral QoL measures (as BAROS Bariatric Analysis and Reporting Outcome System)(12) together with the patients' own intervention were evaluated before the procedure and at the follow-up visits at T1, T3, T6, T12 and T18.

Endpoints

The primary endpoint was the change from baseline in the main weight loss parameter, that is the percentage of total body weight loss (TBWL, %) in the three groups. Secondary endpoints were the percentage of excess weight loss (EWL, %), the evaluation of feasibility in terms of technical success rate and safety in terms of occurrence of serious adverse events(13) and intra or post-procedural adverse events; technical features of each EG procedure, and changes from baseline in anthropometric data, body composition, levels of plasma cholesterol, triglycerides, fasting plasma glucose and glycated hemoglobin, arterial blood pressure, hepatic steatosis and QoL.

Intra-procedural AEs were bleeding, gastric mucosal damage/abrasion, or any other pharyngo-esophago-gastro-duodenal damage procedure-related requiring additional endoscopic therapy or prolonged hospitalization.

Post-procedural AEs were epigastric pain, nausea and vomiting, or any other issues (i.e., electrolyte imbalance, chest pain) requiring additional medical/endoscopic therapy or clinical investigation during hospitalization or until 6 months follow-up.

Pain was measured by the numerical rating scale (NRS)(14), while nausea and vomiting were evaluated by the post-operative nausea and vomiting (PONV)(15,16) scale; both NRS and PONV scales were measured at 6- and 24-hours during hospitalization and at T1, T3 and T6.

Major technical issues were suture system disruption/malfunction or any other technical problem affecting the end of the procedure.

Minor technical issues were events related to the device or the technique not affecting the completion of the procedure (e.g., suture's wire break, an inability to grasp the tissue, or mucosal entrapment in the grasper).

Sample size calculation

The sample size was calculated using a balanced one-way analysis of variance test (ANOVA F-test) under the null hypothesis of treatment equivalence, assuming a moderate effect size (Cohen's f = 0.25), 5% significance level and 80% power based on clinical considerations. This gave 53 patients per group (159 patients overall). However, to compensate for potential drop-out, enrollment was continued beyond the planned sample size, with patients allocated to accessible procedures at the time of enrolment.

Statistical analysis

Patients' characteristics and technical outcomes were summarized using counts and percentages for categorical variables, and means with standard deviations (SD) for continuous variables. The association between dropout and treatment group at T6, T12 and T18 was tested for by chi-squared tests. Differences among the three groups (pairwise or overall) in terms of the technical outcomes were tested for by t-tests or ANOVA F-tests for continuous variables, and by chi-squared tests for discrete variables.

The Pearson's correlation coefficient (rho) and the associated t-test were calculated to evaluate the association between the number of technical issues and procedure time.

Pairwise differences among the three groups in terms of the primary endpoint (TBWL) as evaluated at 6, 12, and 18 months were assessed using weighted least squares (WLS) mean regression(17) to account for unequal variances within groups, while overall differences between all three groups were assessed via a likelihood ratio test (LRT). Additionally, median regression with non-identically

distributed errors(18) was fitted to assess the robustness of the mean estimates. Longitudinal changes of the primary endpoint during all available time points (T1, T3, T6, T12, T18) were assessed using linear mixed-effects (LME) regression(17) and mixed-effects median regression (LQMM)(19). Analogous analyses were carried out for the secondary endpoints (EWL, technical success rate, serious adverse events rate, intra or post-procedural adverse events rate, laboratory analysis, nutritional tests, radiological tests, psychological tests).
As some patients were lost to follow-up, a sensitivity analysis was performed to evaluate the results from the WLS regression for the primary endpoints under the assumption of missing-at-random. Multivariate imputation by chained equations (MICE) with 20 imputations and 10 chain iterations was run on 144 variables collecting treatment and demographic information as well as all available laboratory, nutritional, radiological, psychological, and anthropometric information.
All the analyses were carried out using the R language and environment for statistical computing version 4.4.1(20). The regression models were fitted using the R packages nlme(17), quantreg(21), and lqmm(19), while imputation was carried out by means of the R package mice(22). Statistical significance was set at the 5% level. Additional technical details of the regression models, along with analytical results, are given in Supplementary Materials.

RESULTS

Patients
Overall, 184 out of 203 patients underwent EG through ESG (64 patients), EVG (65) or POSE-2 (55) (Figure 1). The follow-up was attended by 103/184 (56%), 60/184 (32.6%) and 29/184 (15.8%) patients at T6, T12 and T18, respectively. The ensuing dropout rates were not associated with treatment group at any of the above time points ($p \geq 0.4$). Overall, preprocedural body mass index was 36.5 ± 3.0 kg/m^2 (Table 1).

Follow-up and outcomes
Weight loss
Patients experienced 15.5% ± 6.0% (T6), 14.5% ± 8.5% (T12) and 17.1% ± 10.2% (T18) total body weight loss (TBWL) and 39.3% ± 15.5% (T6), 36.7% ± 21.4% (T12), and 43.0% ± 26.6% (T18) excess weight loss (EWL) (Figure 2), with no statistically significant difference among the three techniques in both outcomes at T6 (LRT $p = 0.71$ for TBWL and $p = 0.36$ for EWL), or T12 (LRT $p = 0.56$ for TBWL and $p = 0.46$ for EWL), or T18 (LRT $p = 0.62$ for TBWL and $p = 0.94$ for EWL). Both outcomes decreased significantly over time ($p < 0.001$) with no statistically significant differences among the three groups (Supp. Table 1b). Pairwise comparisons between groups at T6, T12 or T18 did not reach statistical significance (Supp. Table 1a).
One hundred out of one hundred and three patients (97%), 46/60 (77%) and 24/29 (84%) patients achieved at least 5% TBWL, while 89/103 (86%), 40/60 (67%) and 23/29 (79%) achieved at least 25% EWL in the EG group at T6, T12 and T18.

Anthropometric measurements and body composition
All the body measurements decreased in a similar manner over time ($p < 0.001$) with no statistically significant differences among the three groups (Supp. Tables 2b, 3b, 4b, 5b and Supp. Figure 1). Pairwise comparisons between groups at T6, T12 and T18 were also broadly statistically non-significant (Supp. Tables 2a, 3a, 4a, 5a). As for body composition, fat mass and percentage of fat mass significantly decreased ($p < 0.001$), while the percentage of free-fat mass and body cell mass increased ($p < 0.001$), again, with no statistically significant differences among the three groups, longitudinally (Supp. Tables 6b, 7b, 8b and Supp. Figure 2) or cross-sectionally (Supp. Tables 6a, 7a, 8a).

Endoscopic gastroplasty

All procedures were carried out successfully (Figure 3). Overall, the mean procedure time was 59.4 ± 18.5 min; however, it was significantly ($p < 0.001$) longer in the EVG group (72.0 ± 18.3 min) compared to the other two procedures (53.9 ± 14.5 min in ESG and 52.2 ± 16.2 min in POSE-2) (Table 2 and Figure 4).

The overall mean stomach shortening was 12.2 ± 4.0 cm, with a mean percentage length reduction equal to 35.9% ± 10.6%, significantly higher for POSE-2 than ESG ($p = 0.001$) and EVG ($p<0.001$) (Table 2 and Figure 4).

Two serious adverse events were detected (1.1%): one occurred after EVG due to a temporary device entrapment in a right hypertrophic tonsil, while withdrawing the suture system at the end of the procedure; this event required a precautionary intensive care unit admission and one more day than the regular hospitalization. The second was stomach bleeding 12 hours after ESG, that required a second look gastroscopy and treatment by adrenaline and one more day than the regular hospitalization. A mild intra-operative bleeding was observed in 62.0% patients, being self-limited or well managed by cinching the suture, with no significant group differences (Table 2).

As for early (24 hours) post-procedural AEs, 164/184 (89.1%) patients reported experiencing pain, nausea, or vomiting, with no significant group differences.

Pain was mild and stable at 6 and 24 hours, except for a slight, statistically non-significant increase in POSE-2 (Figure 5).

Nausea and/or vomiting were recorded in 130/184 (70.7%) patients and were considered mild in most cases with no difference among the three groups. A clinically relevant PONV (score ≥5) at 24 hours was detected in a few cases (15.7%), with POSE-2 being responsible for most of them, marked by a statistically significant increase between 6 and 24 hours (Figure 5).

At 1-month follow-up, 6 patients (2 in ESG, 2 in EVG and 2 in POSE-2) complained mild epigastric pain, that disappeared at 3 and 6-months follow-up; no other late post procedural AEs were detected.

Minor intraprocedural technical issues occurred in 98/184 (53.3%) patients, more frequently in ESG (50/64) compared to other two procedures, (POSE-2 14/55, $p=0.004$ and EVG 34/65, $p=0.008$). ESG-related minor intraprocedural technical issues were the inability to pass the needle through the tissue (47.5%), wire break while cinching the suture (12.5%), entrapment of the helix in the tissue (7.5%) or accidental needle release while performing the running suture (5%). Minor EVG intraprocedural technical issues were wire break while cinching the suture (47.5%), difficulty while catching or releasing the wire by the monofilament snare after tissue apposition (32.5%), submucosal tag migration (27.5%), difficulty grasping the tissue (12.5%) with a subsequent mucosal abrasion. POSE-2-related minor intraprocedural technical issues were tissue grasper entrapment while unscrewing, inability of the needle to pass through the tissue because of the needle misalignment (5%).

The number of technical issues was correlated with the procedure time ($rho = 0.548$, $p < 0.001$).

No re-hospitalization was needed.

Blood tests and blood pressure

Levels of triglycerides decreased over the 18 months after the EG procedure ($p = 0.002$), with no difference among the three groups, while plasma cholesterol, fasting plasma glucose, glycated hemoglobin and blood pressure remained stable (Supp. Tables 9b, 10b, 11b, 12b and Supp. Figure 3). Pairwise comparisons between groups at T6, T12 and T18 were also broadly statistically non-significant (Supp. Tables 9a, 10a, 11a, 12a).

Elastography and transit study examination

Overall fatty liver disease improved, with a statistically significant decrease from T0 to T3 in ESG ($p = 0.007$), and a similar change in the other two groups. Mean values went from 20.5 at T0 to 14.9 at

T3 (ESG), from 21.1 to 14.3 (EVG), and from 25.4 to 13.3 kPa (POSE-2) (Figure 6 and Supp. Table 13).

Quality of life

The QoL measured by Baros and TSD-OC test improved over time during the 18-month follow-up in ESG ($p < 0.001$), with a similar change in the other two groups (Figure 7 and Supp. Table 14b). Pairwise comparisons between groups at T6, T12 and T18 were also statistically non-significant (Supp. Table 14a).

Sensitivity analyses

The results were insensitive to the use of median regression as well as to the use of multiple imputation.

DISCUSSION

The findings of this study, along with evidence from prior research, underscore the critical role of EG techniques - ESG, EVG, and POSE-2 - in the effective management of obesity. These techniques, which focus on gastric body reduction while sparing the fundus and antrum, have consistently proven to be safe and effective for obese patients, achieving significant weight loss and improving both metabolic parameters and quality of life.

Previous analyses, both retrospective and prospective(23–36), have highlighted the ability of these methods to reduce BMI, TBWL%, and EWL%, as well as mitigate metabolic complications. ESG has shown promise, with studies confirming its safety and sustained efficacy up to five years post-procedure(37).

Comparative meta-analyses of EBTs have reinforced the superiority of endoscopic techniques - excluding gas-filled balloons and botulinum toxin injection - over lifestyle modifications for short-term weight loss(38). While ESG has generally demonstrated superior outcomes compared to older POSE versions, such as POSE-1, these findings may not fully account for advancements in the newer POSE-2 iteration(39,40).

In our randomized trial, comparing ESG, EVG, and POSE-2, we observed no statistically significant differences in feasibility, safety, or efficacy among the three techniques. All were equally effective in achieving weight loss, with most patients attaining at least 5% TBWL and 25% EWL. Anthropometric improvements included reductions in fat mass and increases in free-fat mass percentage, as well as significant declines in body circumferences and triglyceride levels. Quality of life, assessed through standardized measures, improved consistently across all groups at 18 months, further supporting the holistic benefits of these procedures.

While POSE-2 achieved greater gastric shortening, this technical difference did not translate into superior weight loss or quality-of-life outcomes. However, POSE-2 was associated with higher rates of post-operative nausea and vomiting (PONV), which may influence recovery and patient satisfaction in the post-operative. Minor technical issues, such as suture malfunctions, were more common in ESG and EVG but were manageable and did not impact procedural completion, emphasizing the importance of operator expertise in minimizing complications and optimizing outcomes.

To our knowledge, this is the first study to compare three different EG techniques, randomly assigned, within the same clinical setting, providing a direct, head-to-head evaluation of their characteristics and outcomes. A direct comparison between different techniques provides valuable data to develop clearer clinical guidelines, reduce inter-center variability, and support evidence-based procedural decision-making. Regardless of their procedural differences, the similar clinical outcome highlights the flexibility and adaptability of EG approaches in clinical practice. Notably, our study cohort's geographic and genetic homogeneity (Sardinia Island) offered consistency but may limit broader applicability. Moreover, we did not consider patients undergoing GLP-1 therapy, ensuring that the efficacy of EG techniques was evaluated without the confounding factor of pharmacological treatment. Consequently, EGs were assessed solely based on their intrinsic effectiveness.

Despite its strengths, our study has limitations. The pragmatic, single-centre nature of the study, rooted in real-world care, influenced both cohort size and follow-up completeness (15.8% of patients at long term follow-up, 18 months).

The sample size, although adequately powered to test the null hypothesis of equivalence between treatments, was affected by substantial attrition despite additional enrollment, while the single-center design limits the generalizability of findings. Declining follow-up attendance, particularly at 18 months, raises concerns about the accuracy of outcome assessments. Patient dropout after EG and other bariatric therapies remains a critical issue, particularly in medium- and long-term follow-up. While early attrition may stem from procedural factors, psychological components (low motivation, high levels of anxiety, depression, and impulsivity) and logistical barriers often drive disengagement over time(41,42). Furthermore, poor insight into the chronic nature of obesity contributes to a false sense of resolution after initial weight loss(43). In these settings, dropout is not just a clinical issue - it is a behavioral one. A sustained sense of urgency and structured psychological support are crucial to counteract the tendency toward disengagement once early goals are met. Concerning this study, our decision not to collect telephone interviews from patients who did not attend follow-up visits, focusing only on those who were physically present, may have affected further lack of data. To reduce the adverse consequences of missing data, we applied multiple imputation under the assumption of missing at random (MAR), the plausibility of which was supported by the inclusion of a large number (144) of auxiliary variables. Multiple imputation not only yields larger standard errors that reflect the uncertainty due to missingness, but it also corrects for potential bias, thereby improving the reliability of the results despite the incomplete dataset. Under the MAR assumption, the longitudinal analysis results—showing non-differential outcome improvement over time—can be considered reliable, as LME regression is generally robust(44) in this context. While self-selection cannot be ruled out, comparable dropout rates across the three groups suggest no preferential bias, supporting the validity of the comparisons among groups.

Another limitation is that the number of POSE-2 procedures performed was lower than expected due to production issues with the device from the manufacturing company during the study period. This limitation may have reduced the comparative efficiency of the follow-up estimates but it did not affect the original sample size requirement, which was met at baseline, nor does it represent a source of bias insofar the dropout mechanism is non-preferential as discussed above.

Future research should explore the integration of EG techniques with personalized medical therapies tailored to patient phenotypes, in line with the emerging paradigm of precision medicine in obesity management. Genetic and environmental factors likely play a pivotal role in determining the most effective combination of endoscopic and pharmacological treatments for individual patients(45,46).

Clinically, ESG and POSE-2 may be preferred in patients requiring shorter procedure time (i.e. patients at risk with prolonged anesthesia), and ESG or EVG may also be considered in patients particularly intolerant to postoperative pain (e.g. those with chronic pain, preoperative anxiety, or opioid tolerance). POSE-2 may be advantageous when greater gastric shortening is desired (i.e. patients with markedly enlarged stomachs). Another reason for choosing one device over another could be the economic factor, namely the price, which remains variable depending also on the number

of accessories used (wires, forceps, etc.) and the market price in the different countries. In our case, the average cost for device and accessories was approximately equivalent. From a technical standpoint, ESG showed a higher number of minor technical complications. Therefore, EVG and POSE-2 may be preferable for less experienced operators, in order to reduce the risk of unexpected minor complications.

From a practical perspective, EVG requires the active participation of two equally skilled operators. By contrast, the role of the second operator is rather marginal in ESG and POSE-2. In ESG, the assistant's task is limited to handling the helix device, while in POSE-2 the second operator is only responsible for maneuvering the ultrathin endoscope used exclusively for visualization. Conversely, in EVG the assistant plays a critical role in managing the entire device and performing the tissue puncture, as detailed in the Supplementary material on procedural aspects.

In conclusion, in this single-center study ESG, EVG, and POSE-2 appeared similarly safe, effective, and feasible for obesity treatment in the short- and medium-term; however, since the study was designed with the objective to detect any difference, without specifying a preferred treatment, it was not powered for formal equivalence testing. Moreover, high attrition rates limit the reliability of longer-term weight loss outcomes. Nevertheless, given the intrinsic features of each device and the heterogeneity of patient profiles, one procedure may be more suitable than another in specific scenarios. Thus, the choice of technique should be individualized and carefully tailored to patient characteristics and procedural considerations within the framework of personalized obesity therapy.

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Table 1. Patients' characteristics at baseline.

Characteristics	**Overall (N = 184)**	**ESG (N = 64)**	**EVG (N = 65)**	**POSE-2 (N = 55)**
Age, years	45 ± 10	44.3 ± 9.9	46.9 ± 10.1	44.7 ± 9.8
Sex, female	165 (87.3)	55 (87.3)	55 (87.3)	55 (87.3)
Preprocedural weight, kg	94.0 (11.5)	95.0 (13.3)	93.6 (11.1)	93.4 (9.9)
Preprocedural body mass index, kg/m^2	36.5 ± 3.0	36.1 ± 2.9	36.8 ± 2.8	36.5 ± 3.2
Obesity class				
Obesity class I	61 (32.3)	22 (36.0)	19 (31.1)	20 (32.8)
Obesity class II	110 (58.2)	35 (55.5)	39 (61.9)	36 (57.1)
Obesity class III	18 (9.5)	6 (9.5)	6 (9.5)	6 (9.5)
Fatty Liver disease	133 (70.3)			
Kidney microlithiasis	67 (35.4)			
Hypertension	39 (20.6)			
Arthropathy	37 (19.6)			
Hyperlipidemia	25 (13.2)			
Endocrine diseases	23 (12.2)			
Anxious depressive syndrome	18 (9.5)			
Obstructive sleep apnea	13 (6.9)			
Fibromyalgia	11 (5.8)			
Gastroesophageal reflux disease	11 (5.8)			
Heart failure	5 (2.6)			
Type 2 diabetes mellitus	3 (1.6)			

Values are counts (%) or mean ± standard deviation.

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Table 2. Technical outcomes.

	Overall	**ESG**	**EVG**	**POSE-2**	**p-value**			
	(N = 184)	**(N = 64)**	**(N = 65)**	**(N = 55)**	**Overall**	**ESG vs EVG**	**ESG vs POSE-2**	**EVG vs POSE-2**
Completion	184 (100.0)	64 (100.0)	65 (100.0)	55 (100.0)	NA	NA	NA	NA
SAE	2 (1.1)	1 (1.6)	1 (1.5)	0 (0.0)	0.9 (0.65)	1.000	1.000	1.000
Intraprocedural AEs	114 (62.0)	50 (78.1)	34 (52.3)	30 (54.5)	10.9 (0.004)	0.004	0.011	0.951
Mild bleeding	114 (62.0)	50 (78.1)	34 (52.3)	30 (54.5)	10.9 (0.004)	0.004	0.011	0.951
Submucosal edema	21 (11.4)	10 (15.6)	5 (7.7)	6 (10.9)	2 (0.363)	0.258	0.630	0.771
Post-procedural AEs	164 (89.1)	57 (89.1)	59 (90.8)	48 (87.3)	0.4 (0.828)	0.976	0.987	0.749
Pain	136 (73.9)	44 (68.8)	51 (78.5)	41 (74.5)	1.6 (0.451)	0.293	0.621	0.773
NRS 6h	3.0 ± 3.2	2.8 ± 3.3	3.1 ± 3.1	3.0 ± 3.0	0.1 (0.916)	0.688	0.767	0.921
NRS 24h	2.9 ± 2.6	2.5 ± 2.5	2.6 ± 2.5	3.7 ± 2.8	2.6 (0.076)	0.963	0.045	0.052
Nausea	119 (64.7)	45 (70.3)	37 (56.9)	37 (67.3)	2.8 (0.251)	0.162	0.874	0.330
Vomiting	92 (50.0)	31 (48.4)	31 (47.7)	30 (54.5)	0.7 (0.721)	1.000	0.631	0.572
PONV scale 6h	1.3 ± 1.6	1.5 ± 1.6	1.2 ± 1.7	1.1 ± 1.5	0.5 (0.588)	0.425	0.332	0.852
PONV scale 24h	1.7 ± 1.8	1.3 ± 1.2	1.4 ± 1.8	2.4 ± 2.0	4.7 (0.011)	0.715	0.006	0.015
Major technical issues	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Minor technical issues	98 (53.3)	50 (78.1)	34 (53.1)	14 (25.5)	31.7 (0)	0.008	0.004	0.000
Procedure time (min)	59.4 ± 18.5	53.9 ± 14.5	72.0 ± 18.3	52.2 ± 16.2	18.7 (<0.001)	< 0.001	0.639	< 0.001
Bites per procedure	19.0 ± 6.6	28.0 ± 5.3	14.2 ± 2.3	16.8 ± 1.9	165.7 (<0.001)	< 0.001	< 0.001	0.001
SLR (%)	35.9 ± 10.6	33.6 ± 11.2	32.9 ± 10.0	41.4 ± 8.7	8.9 (<0.001)	0.769	0.001	< 0.001
1-day hospitalization	182 (98.9)	63 (98.4)	64 (98.5)	55 (100.0)	0.9 (0.65)	1.000	1.000	1.000

Values are counts (%) or mean ± standard deviation. SAE: serious adverse events; AEs: adverse events; NRS: numeric rating scale; PONV: post operative nausea and vomiting; SLR: stomach length reduction.

Figure 1. Flow chart of study participants (randomization and enrolment).

Figure 1. Total body weight loss (TBWL, %) and excess weight loss (EWL, %) during 18 months of follow-up.

Figure 3. Appearance of gastric body after Endoscopic Gastroplasty through endoscopic sleeve gastroplasty (ESG, left), endoscopic vertical gastroplasty (EVG, center) or distal primary obesity surgery endoluminal (POSE-2, right), respectively.

Figure 4. Boxplots of (left) procedure time (min) and (right) stomach shortening (%).

Figure 2. Mean and standard error at 6 and 24 hours for (left) numeric rating scale (NRS) and (right) post operative nausea and vomiting (PONV).

Figure 3. Hepatic steatosis between baseline and 3 months follow-up.

Figure 4. Baros test during 18 months follow-up.

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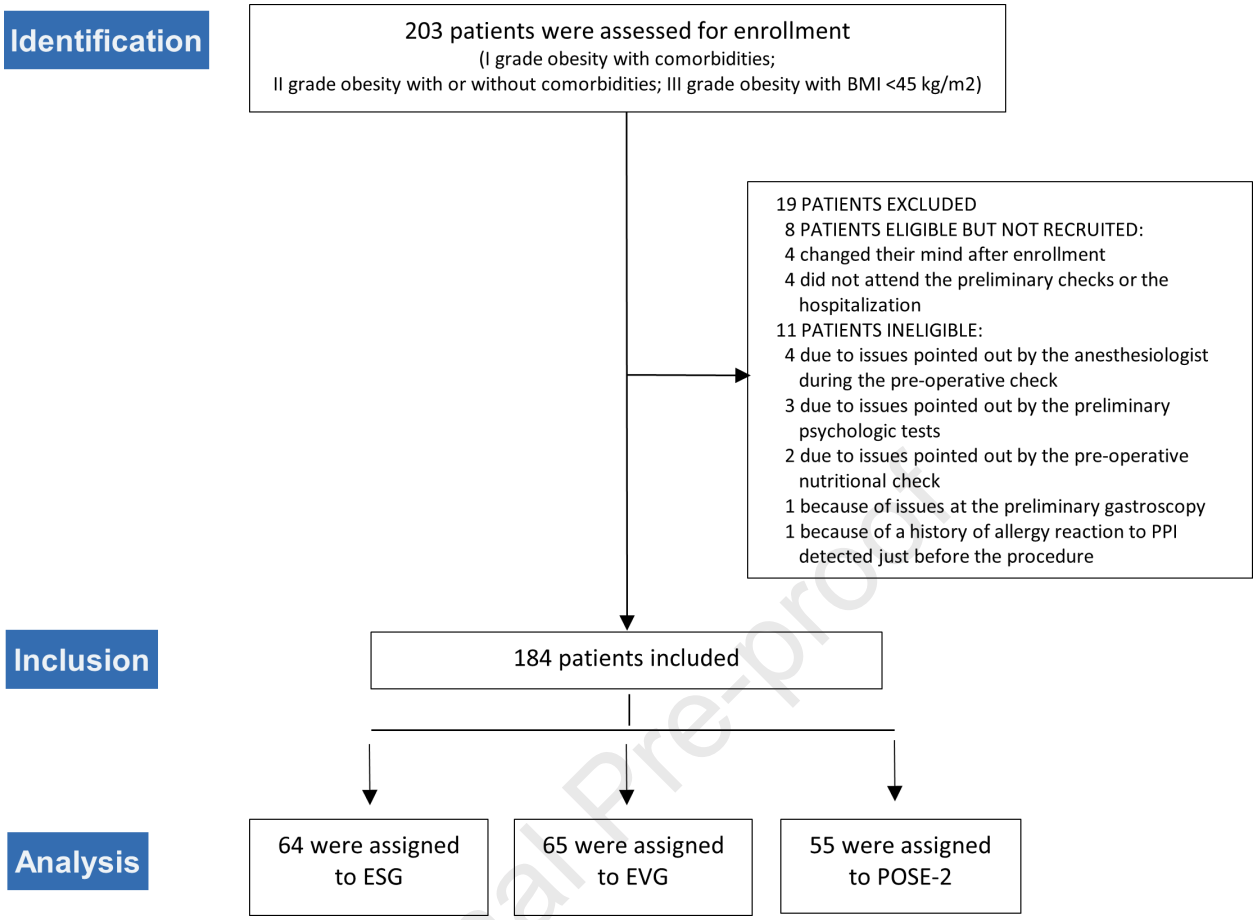

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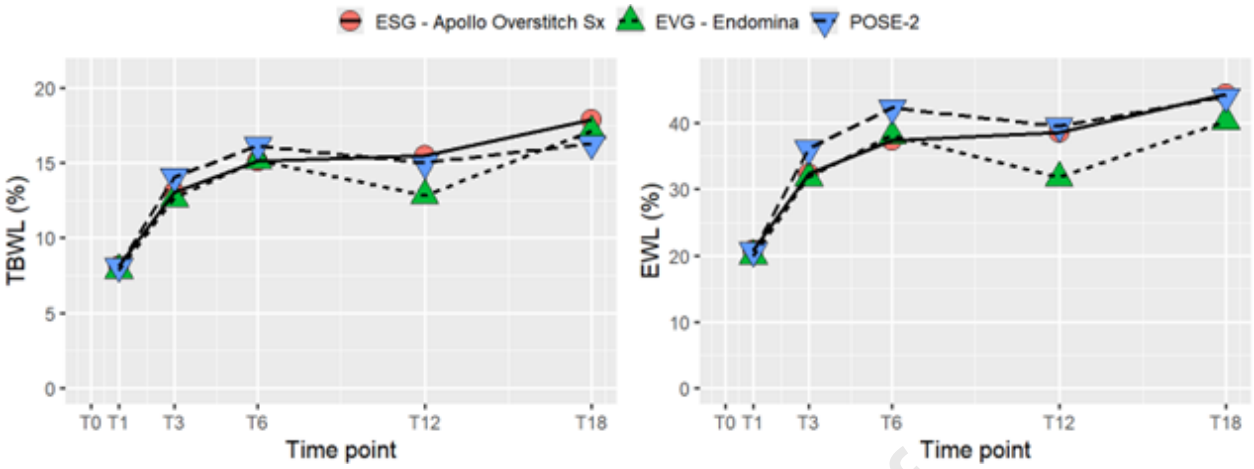

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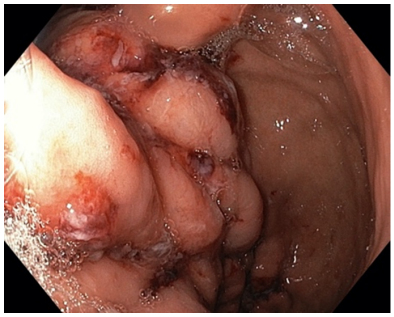
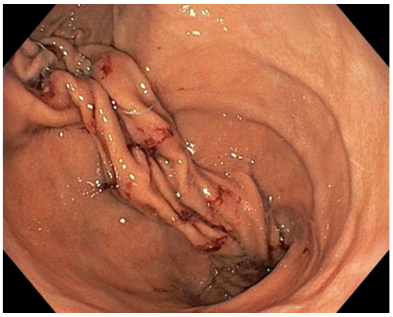
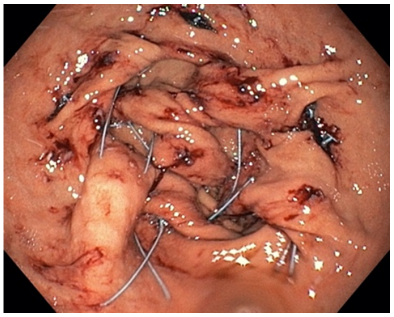

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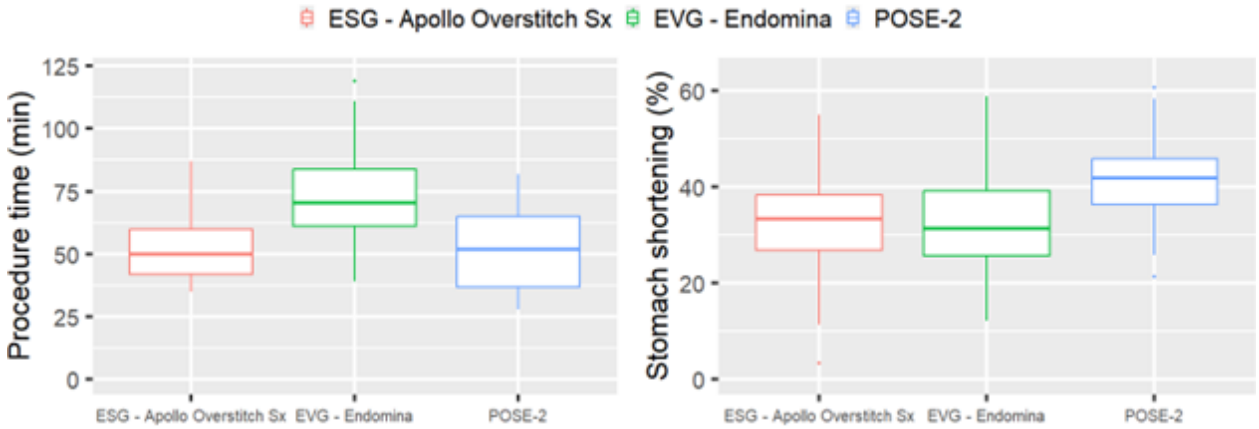

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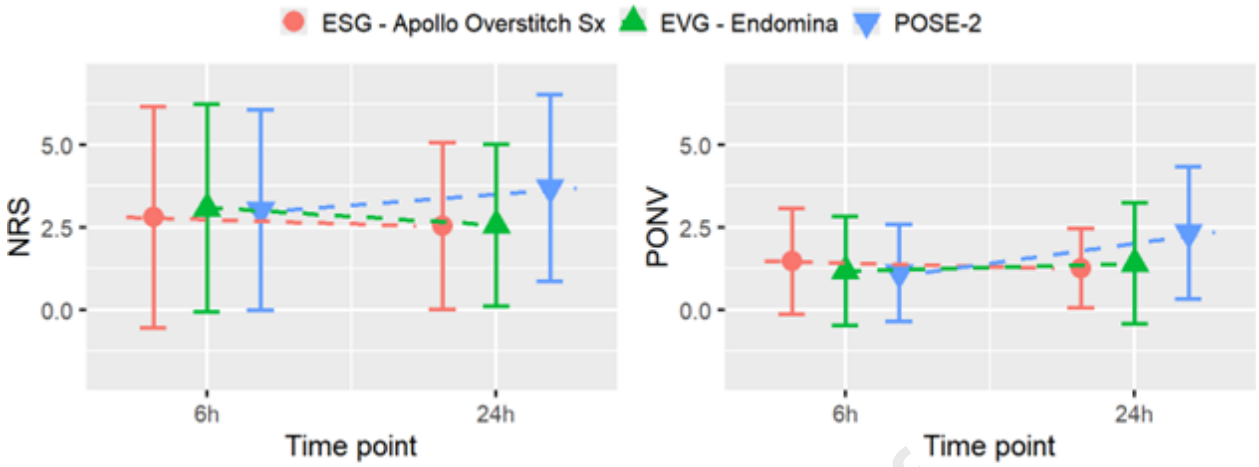

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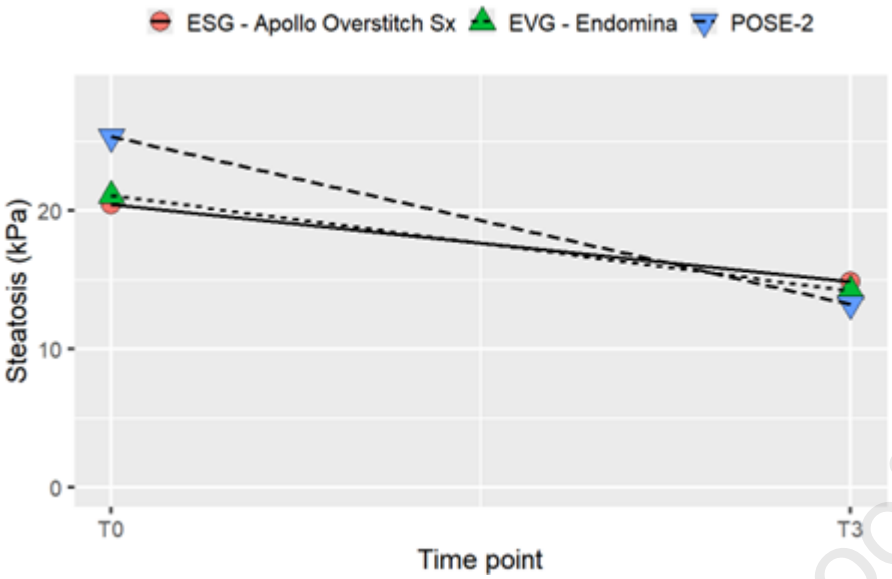

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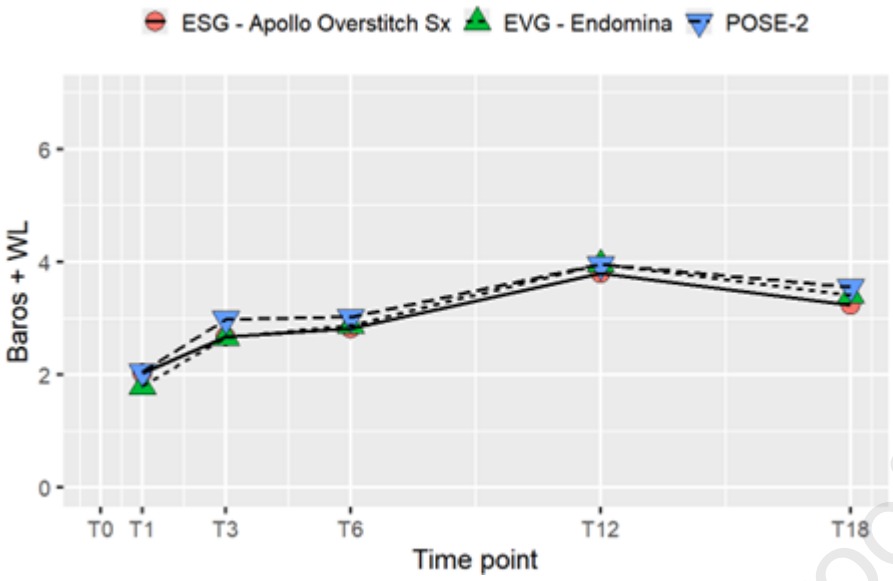

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ACRONYMS AND ABBREVIATIONS

EBTs: Endoscopic bariatric therapies

EG: Endoscopic Gastroplasty

ESG: endoscopic sleeve gastroplasty

EVG: endoluminal vertical gastroplasty

POSE-2: primary obesity surgery endoluminal-2

TSD-OC: SIO-Obesity correlated Disability Test

BAROS: Bariatric Analysis and Reporting Outcome System

AEs: adverse events

TBWL: Total Body Weight Loss

EWL: Excess Weight Loss

QoL: Quality of Life

BMI: body mass index

PONV: post-operative nausea and vomiting

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RUNNING HEAD

Endoscopic gastroplasty techniques: a randomized trial

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