Cleveland Clinic
Digestive Disease Institute

Comparing Outcomes of Classic Transoral Outlet Reduction (TORe) Versus Endoscopic Submucosal Dissection-TORe: A Randomized Controlled Trial

IRB Approval Number: 23-886

Approval Date: 09/22/2023

Title: Comparing Outcomes of Classic Transoral Outlet Reduction (TORe) Versus Endoscopic Submucosal Dissection-TORe: A Randomized Controlled Trial

Short Title: Comparing Reduction with ESD- versus APC-TORe (CREATORe)

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1 Background/Scientific Rationale

1.1 Background

Roux-en-Y gastric bypass (RYGB) is the second-most common bariatric surgery performed in the U.S., with over 41,000 procedures performed in 2020.[1] Despite well-established efficacy on weight reduction, a proportion of patients will experience insufficient weight loss (IWL) or weight regain (WR) following surgery. In fact, 20-25% of patients post-RYGB will experience significant WR after reaching nadir weight.[2, 3] While etiology of WR is multifactorial, dietary indiscretion, behavioral eating patterns, dysphagia, genetics, and anatomical considerations including gastrogastric fistulae and dilated gastrojejunal anastomoses (GJA) have been identified as determinants.[4-7]

GJA dilation has long been considered a significant factor in post-RYGB weight regain among the bariatric surgery community. Various attempts at surgically reinforcing the anastomosis via "banded" techniques have been developed, with improved outcomes.[8] With the advent of endoscopic suturing devices, the transoral outlet reduction (TORe) was developed, whereby the dilated GJA is luminally sutured in a purse string fashion and cinched down to greatly reduce the diameter completely endoscopically. This technique was proven successful for inducing weight loss in a 2013 prospective, randomized, sham-controlled trial (RESTORe).[9] As technical variations advanced, sclerotherapy utilizing argon plasma coagulation (APC) electrocoagulation to promote tissue contraction and adhesion in addition to endoscopic suturing has become widely utilized as the traditional or "classic" TORe (c-TORe). The TORe procedure is currently standard of care and one of the alternative treatments for obesity and WR after RYGB.

Multiple analyses consistently report 8-9% TBWL at 1 year following c-TORe.[10-12] However more recently, the endoscopic submucosal dissection (ESD)-TORe (E-TORe) was developed in attempts to improve this benchmark. The E-TORe employs continuous ESD around the gastric side GJA in addition to APC prior to endoscopic suturing. In the only retrospective analysis comparing c-TORe to E-TORe, E-TORe was shown to achieve superior weight loss over c-TORe at 1 year (12.1±9.3% TBWL vs 7.5±3.3% TWL [p=0.036]).[13] E-TORe was further noted to be a significant predictor of %TBWL after controlling for age, sex, BMI, weight regain and years from RYGB on regression analysis. This study is, however, limited by the small sample size, retrospective nature and wide standard deviation of the results, warranting further investigation.

As technical and technological advances continue to expand the realm of endoscopic bariatric and metabolic therapy, it is imperative that these various techniques are adequately compared to afford completely informed decision making for both patients and providers. To date, no prospective studies have compared the c-TORe with E-TORe. As such, we propose a prospective, randomized controlled trial comparing outcomes of c-TORe and E-TORe in patients with WR after RGYB.

1.2 Rationale

Endoscopic bariatric surgery revisions for IWL or WR are increasingly utilized due to their minimally-invasive nature, effectiveness and safety. The c-TORe is the most widely employed endoscopic revision, however recent limited data demonstrates increased weight loss following E-TORe compared to c-TORe, with equivalent safety profiles. As this may represent the next frontier in endoscopic revision of RYGB, it is imperative that these two techniques are adequately compared through a prospective trial.

2 Study Objectives

2.1 Objective/Hypothesis:

We hypothesize that E-TORe results in superior weight loss at 6 and 12 months compared to c-TORe.

2.2 Aim (s)

1. To compare weight loss following E-TORe and c-TORe in patients with history of RYGB and WR with dilated GJA.
2. To compare rates of technical success and adverse events following E-TORe and c-TORe

2.3 Clinical Relevance/Impact

Results from this analysis may impact current endoscopic bariatric surgery revision strategies and promote or refute a change in practical tendencies away from c-TORe and toward E-TORe. Additionally, if E-TORe is confirmed superior, this shift may result in improved weight loss for applicable future patients and overall improved metabolic outcomes.

3 Subject Selection

3.1 Inclusion Criteria

Adult patients who have undergone RYGB with documented WR and a dilated GJA who are interested and appropriate for endoscopic revision (TORe) as per current standard of care will be eligible for inclusion.

3.2 Exclusion Criteria

1. Prior revision of gastric bypass
2. Active and uncontrolled gastro-esophageal reflux disease defined as ≥ grade C esophagitis
3. Active untreated Helicobacter pylori infection
4. Malignancy newly diagnosed by endoscopy
5. Upper gastro-intestinal conditions such as ulcers, polyps, gastric varices, strictures, congenital or acquired intestinal telangiectasia or other abnormalities that preclude completion of TORe
6. Presence of gastrogastric or gastroenteric fistula
7. Inability to undergo general anesthesia
8. Participating in another ongoing clinical trial of an investigational weight loss drug or device
9. Active pregnancy
10. Use of anticoagulation therapy or P2Y12 inhibitors which cannot be discontinued for the time frame surrounding the procedure
11. Insulin-dependent diabetes mellitus
12. Unwillingness to comply with standard post-TORe dietary guidelines and follow-up care
13. Any other anatomical, technical or otherwise factor that limits the ability of the endoscopist to perform either E-TORe or c-TORe
14. Any additional factor, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the trial protocol

4 Study Design

4.1 Study setting

We will perform a prospective, single-blinded, randomized controlled trial of patients who have a history of RYGB with WR and a dilated GJA who undergo endoscopic revision at the Cleveland Clinic (as per standard of care) from the date of approval of the IRB and forward. The study will compare outcomes following E-TORe (case) and c-TORe (control). We will prospectively maintain the database in the REDCap platform and EPIC electronic medical records with the inclusion criteria as below.

Definitions:

- Weight regain: regain of ≥10% total body weight (TBW) or ≥25% excess body weight (EBW) from post-RYGB nadir
- Dilated gastrojejunal anastomosis: ≥15mm diameter
- %TBWL: calculated as follows:

(pre-TORe weight – post-TORe weight)/pre-TORe weight x 100

- Adverse events: defined and graded by severity as per the ASGE lexicon[14]
    - Mild: procedure aborted due to the event or unplanned admission of 3 nights or less
    - Moderate: unplanned admission of 4 to 10 nights, intensive care unit (ICU) admission for 1 night, or when transfusion, repeat endoscopy, or interventional radiology procedure is required
    - Severe: unplanned admission of greater than 10 nights, ICU admission for greater than 1 night or surgery required to address the AE
    - Fatal: death occurred due to the event
- Technical success: successful completion of TORe procedure as determined by performing endoscopist

Inclusion criteria:

- Adult patients with history of RYGB and WR
- Dilated GJA as diagnosed on endoscopy
- Patients undergoing standard of care for treatment of obesity with endoscopic revisional procedure (a.k.a. TORe) who are enrolled in the GI Bariatric Endoscopy program and clinic

Exclusion criteria:

- Prior revision of gastric bypass
- Active and uncontrolled gastro-esophageal reflux disease defined as ≥ grade C esophagitis
- Active untreated Helicobacter pylori infection
- Malignancy newly diagnosed by endoscopy
- Upper gastro-intestinal conditions such as ulcers, polyps, gastric varices, strictures, congenital or acquired intestinal telangiectasia or other abnormalities that preclude completion of TORe
- Presence of gastrogastric or gastroenteric fistula
- Inability to undergo general anesthesia
- Participating in another ongoing clinical trial of an investigational weight loss drug or device
- Active pregnancy
- Use of anticoagulation therapy or P2Y12 inhibitors which cannot be discontinued for the time frame surrounding the procedure
- Insulin-dependent diabetes mellitus
- Unwillingness to comply with standard post-TORe dietary guidelines and follow-up care
- Any other anatomical, technical or otherwise factor that limits the ability of the endoscopist to perform either E-TORe or c-TORe
- Any additional factor, which in the investigator's opinion, might jeopardize the subject's safety or compliance with the trial protocol

4.2 Randomization Method and Blinding

All enrolled subjects will undergo TORe procedure. Patients with a history of RYGB who are referred to the bariatric endoscopy center for WR will be screened for inclusion. As per standards of care, all patients being

considered for TORe will undergo standard esophagogastroduodenoscopy (EGD). Following EGD and application of exclusion criteria, if a patient remains eligible and interested in TORe, they will be provided a copy of the informed consent and the trial will be discussed. Only after signing the informed consent form will the subject be officially enrolled in the trial and randomized to one of two treatment arms: E-TORe or c-TORe. Allocation concealment will be in place to ensure the individual enrolling the subject into the study has no prior knowledge of group assignment. Block randomization will occur with randomly mixed block sizes of either 1, 2 or 3. As the performing endoscopist cannot be blinded to the treatment arm, this cannot be a double-blinded analysis. All practitioners performing standard post-procedural care, including Advanced Practice Providers, dieticians and bariatric psychologists, as well as data analysts, will be blinded to the treatment arm, however.

4.3 Follow-up and Data Collection

Potential trial participants will be screened for candidacy and interest at routine GI/Bariatric Endoscopy referral visits as described above in 4.2. Standard data collected at this initial visit will include patient demographics, medical history, surgical history, social history, vital signs, current body weight/BMI, pre-surgical body weight/BMI, post-surgical body weight/BMI nadir, %TBW regain, and routine pre-procedural laboratory data. If the patient agrees to enroll, these data may be recorded for use in the study.

Following successful completion of either E-TORe or c-TORe, subjects will be admitted to the hospital for overnight monitoring as per standard of care. Standardized post-procedural instructions will be given to admitting teams for all subjects regardless of treatment arm. These will include patient remaining nil per os overnight with slow initiation of liquid diet on post-operative day #1. Additionally, aggressive anti-emetic regimens will be prescribed to avoid post-procedural retching or emesis, placing the integrity of the sutures at risk. Please see the Appendix for full list of instructions utilized for the duration of post-procedural inpatient monitoring. These instructions are standard of care for all post-TORe patients and are utilized for all patients undergoing TORe procedure at the Cleveland Clinic, regardless of participation in this or any other clinical trials.

Following discharge, all subjects will again follow standard post-TORe follow-up procedures. These include:

- Follow up with bariatric dietician 2 weeks, 6 weeks, 3 months, 6 months, 9 months and 12 months post-procedure. Dieticians will be blinded to treatment arm throughout the duration of the study.
- Follow up in GI/bariatric endoscopy clinic at week 4, week 12, and every 3 months thereafter. GI clinic follow-up visits will be with Advanced Practice Provider(s) that are blinded to the treatment arm throughout the duration of the study.
- Follow up with bariatric psychology at week 4, week 12 and every 3 months thereafter. Further follow up with psychology will be at the discretion of the treating psychologist. The treating psychologist will be blinded to the treatment arm for the duration of the study.

No deviation from standard of care for post-TORe follow-up will be required for the purpose of this study.

For the subjects in this study, chart review will be performed to acquire demographics data, outcomes, physician notes, natural history of the disease, laboratory, imaging tests, procedure and surgery data, and results from the hospital electronic records (powered by EPIC systems corporations 2016).

Data collected during TORe procedure will include:

- GJA diameter, measured using a calibrated, flexible measuring device inserted through the working channel of the endoscope (Olympus, Center Valley, PA, USA)

- Technical approach (E-TORe vs c-TORe)
- Technical success
- Procedure time
- Intra-procedural complications

Data collected at each GI/bariatric endoscopy clinic follow-up will include:
- Current weight/body mass index (BMI)
- Adverse events
- Current medication use

Data collection will continue for a total of 12 months post-TORe procedure.

4.4 End points

Primary:
- %TWBL achieved at 6 and 12 months post-TORe

- Secondary:
  - Rates of technical success
  - Procedural time
  - Rates of adverse events
  - Proportion of subjects who achieved at least 5% TBWL

4.5 Recruitment of patients

Adult patients with history of RYGB referred to the CCF Bariatric Endoscopy program for WR will be screened for inclusion at initial clinic visit. If EGD has been completed at CCF within 12 months prior to the initial visit documenting dilated GJA, this may be used to satisfy inclusion/exclusion criteria. If no recent EGD is available for review, patients will be referred for pre-revision EGD to evaluate potential causes of weight regain (e.g. dilated GJA, gastrogastric fistula, etc.) or other anatomical/physiological considerations, as is standard of care. Once EGD is completed and inclusion/exclusion criteria met (as determined by a member of the clinical trial team), patients will be given a copy of the informed consent form and the trial will be discussed in detail by a trial team member. For subjects who already had recent EGD available for review, this may occur at the initial clinic visit. For those who required EGD (i.e. no recent EGD to evaluate for etiology of weight loss and revisional candidacy), this will occur at a subsequent follow-up clinic visit. Only after a formal explanation of the trial by a Trial Investigator and signing the informed consent form will the subject be enrolled and randomized.

The consent form will be provided as a paper hard copy. Two copies of the consent form will be provided: one to be signed and given to the trial team for secure storage and a second copy for the subject to keep for their records. If desired, a copy of the consent form may also be sent electronically via Epic MyChart for the subject's reference.

The decision whether or not to participate in the trial will have no impact on the candidacy of the patient for endoscopic revision (TORe). Those who choose not to participate in the trial may still be eligible to undergo TORe. For patients who undergo TORe outside of the trial, c-TORe will be employed as is the current standard practice at CCF. Subjects who choose to participate may decide to withdraw at any time, with no punitive risk.

4.6 Intervention

Both treatment arms (c-TORe and E-TORe) will be performed using a standard 2T therapeutic upper endoscope (Olympus, Center Valley, PA, USA) affixed with the endoscopic suturing device (OverStitch™, Apollo Endosurgery, Austin, TX, USA). The OverStitch™ device is FDA approved for endoscopic placement

of sutures via a dual-channel or single-channel endoscope. All components of the system have FDA 510k clearance for use in human subjects. The device will be used within its intended FDA approval and the TORe performed in the standard fashion by an experienced bariatric endoscopist, with the only difference being the use of APC or ESD prior to suturing. Placement of additional gastroplasty sutures within the gastric pouch following GJA outlet reduction for reinforcement and protection of the TORe will be performed at the discretion of the performing bariatric endoscopist, as is standard practice. All procedures will be performed by an experienced bariatric endoscopist with expertise in all aspects of the aforementioned procedures.

c-TORe
The classic "c-TORe" will be completed utilizing APC prior to endoscopic suturing. In this approach, the gastric rim of the anastomosis is circumferentially ablated using APC (forced APC, flow of 0.8 L/min and power of 30-70 watts) extending an average of 1-2 cm from the outlet. Following ablation, endoscopic sutures are placed in a purse string fashion within the ablated area and the outlet cinched closed over a 6mm through-the scope (TTS) balloon.

E-TORe
The "E-TORe" utilizes ESD in addition to APC prior to endoscopic suturing. In this approach, a standardized solution of normal saline or hetastarch mixed with methylene blue and epinephrine is injected into the gastric rim of the GJA outlet. The mucosa is then carefully incised to expose the underlying muscular layer for a width of approximately 1cm around the GJA circumference. Following ESD, APC is then applied to the inner and outer mucosal margins of the ESD tract. Finally, endoscopic sutures are then placed in purse string fashion and cinched closed around a 6mm TTS balloon.

All subjects will follow standard post-procedure care regardless of treatment arm as described in section 4.3 above.

4.7 Consent form
Patient informed consent will be obtained from all patients prior to enrolling in the study. The consent form is attached as per Cleveland Clinic consent template and policy.

4.8 Funding
This randomized controlled trial study has no funding.
All procedures, treatments and clinic visits are per standard of care.
No survey or calls to patients are needed.

5 Statistical Plan
5.1 Statistical Analysis Plan
Data will be described using mean and standard deviation (SD) for normal continuous variables, median and interquartile range (IQR) for non-normal continuous variables, and frequency (percentage) for categorical variables. Shapiro-Wilk test will be used to determine the normality of the continuous variable. Unadjusted Cox proportional hazards (PH) survival analysis will be used to assess the association between clinical factors, including treatment group, and time to heal. The scaled Schoenfeld residual and the Cox-Snell residual will be checked for proportional hazard assumptions and model's goodness-of-fit. The Kaplan-Meier cumulative incidence curve with 95% confidence intervals will be constructed. Statistical analysis will be performed using R (version 3.6.2; Vienna, Austria) and SAS (version 9.4; Cary, NC) software and p-value<0.05 will be considered statistically significant. All analysis will be done with intention-to-treat analysis.

5.2 Sample size calculation
The sample size calculation was performed based on the primary outcome.

There exists very limited data comparing c-TORe to E-TORe from which sample size may be computed. In the only retrospective comparison, a difference of 12.1±9.3% TBWL vs 7.5±3.3% TWL (p = 0.036) was reported (E-TORe vs c-TORe). However, this study contains several limitations and wide margins of error.

In general, a TORe procedure is considered successful if it achieves 8% TBWL and this is corroborated by current literature for c-TORe.[10-12] We consider 2-3% increase in TWBL to be clinically significant, i.e. a mean %TWBL in the treatment arm of 10-11%. The only prior report of E-TORe reports a mean %TWBL of 12.1%, however we chose to use a more conservative figure at 11%. Additionally, as mentioned, the only prior comparison of E-TORe to c-TORe is limited by wide standard deviations. A large, systematic review and meta-analysis of prior TORe reported a pooled %TBWL of 8.55% with 95% CI 5.69-11.4.[12] This corresponds to a standard deviation of ±1.425 (considering 95% of a study population falls within 2 standard deviations of the mean, thus (11.4-8.55)/2 = 1.425). Again, a more conservative standard deviation of 3.5% was chosen for this study.

Therefore, through power calculations utilizing an expected mean %TWBL of 11 ± 3.5% in the E-TORe group compared to 8% in the c-TORe group, with $\alpha = 0.05$ and 80% power ($\beta = 0.2$) in a 1:1 randomization assignment, we would need 21 subjects per group for a total of 42 subjects. Assuming a 30% loss-to-follow-up rate, the total number of subjects required for enrollment is 70.

Currently, 2-3 TORe are completed weekly at Cleveland Clinic Main Campus. If 2.5/week are enrolled, enrollment would take 28 weeks. Thus, the total duration of the study including follow-up would be 28 + 52 = 80 weeks.

5.3 Interim analysis
No interim analysis will be performed. Data will be collected as described throughout the study period and analyzed at study completion (12 months after the last TORe is performed).

6 Safety and Adverse Events
This study compares outcomes of two technical variations of the TORe procedure, both of which are currently utilized at the discretion of performing endoscopists. All pre- and post-procedure care will be the same for each arm, which is standard of care described above. Intraprocedural care – with the exception of performing ESD or not – including anesthesia care, nursing supervision, endoscope utilized, pre-procedural preparation and post-procedural recovery will be identical in the two arms. In their comparison of c-TORe to E-TORe, Jirapinyo et al. report no significant difference in adverse event rate between the two procedures.[13] Thus, we do not anticipate any safety issues resulting from study participation.

We will monitor all procedure-related adverse events as per standard protocol for any endoscopic procedure performed at CCF for the duration of the study. Any such events will be reported to the Cleveland Clinic Institutional Review Board in accordance with proper and responsible conduct of research.

7 Data Management
7.1 Data Management
All trial data will be stored on a secure, password encrypted REDCap (Research Electronic Data Capture) account hosted at the Cleveland Clinic. REDCap is a secure, web-based application designed to support

data capture for research studies, providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures and automated export procedures for data downloads to common statistical packages.[15, 16] Additionally, an encrypted Excel form will be utilized for the randomization process. Only investigators listed on the IRB forms will have access to the REDCap account, encrypted excel forms, and EPIC electronic medical record software containing the data. The REDCap account and EPIC system are secure and HIPAA compliant. Excel sheets will be encrypted and require a password to access. The Digestive Disease and Surgery Institute (DDSI) has extensive experience in the acquisition, maintenance, and analysis of both large and small research studies databases.

7.2 Data Acquisition and Maintenance

Data will be obtained from the EPIC electronic medical record system. All subject data will be collected electronically as detailed in the above sections.

8 Confidentiality

Information about study subjects will be kept confidential, protected and encrypted in REDCap. Informed consent will be obtained from all patients prior to enrollment in the study.

9 Records Retention

The final collected and retained data will be stored in REDCap.

10 Key Words for PubMed

Transoral outlet reduction; TORe; gastric bypass; weight regain

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