Cleveland Clinic
Digestive Disease Institute

OPEN versus InTact Capsule Proton Pump Inhibitors for the Treatment of Marginal Ulcers after Bariatric Surgery (OPEN-IT)

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Title: OPEN versus InTact Capsule Proton Pump Inhibitors for the Treatment of Marginal Ulcers after Bariatric Surgery (OPEN-IT)

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1 Background/Scientific Rationale

1.1 Background

The Roux-en-Y gastric bypass (RYGB) is the second-most performed bariatric procedure in North America, comprising 17.0% of all procedures in 2018.[1] Although the percentage of RYGB has decreased since 2011, the number of cases were stable from 2016 to 2017(40,316 to 40,574, respectively). Furthermore, there has been a trend of reversal; slightly increasing in number of cases from 2017 to 2018 (40,574 to 42,945 respectively). [1] Therefore, it is common to encounter patients with both favorable outcomes and complications of this procedure.

While physiology is poorly understood, marginal ulcer (MU) formation at the gastrojejunal anastomosis is a common complication following RYGB. The incidence of MU formation after surgery is variable, with reported rates ranging from 0.6% to as high as 25%.[2] According to a recent systematic review, 4.6 % of patients developed MU following RYGB. [2,3] Furthermore, approximately 17% of patients with MU require surgical intervention for severe complications such as bleeding, perforation, stricture, and gastrogastric fistula. [4]

Medical treatment with either proton pump inhibitors (PPIs), histamine type-2 (H2) receptor antagonists, mucosal barrier agents (e.g. sucralfate) or a combination of these is the first-line therapy. [5] Of the three, PPI is the treatment of choice for post-operative MU formation. Although PPIs have been utilized for many years, studies investigating the variable forms of medication delivery and their effect on medication response rates are lacking. Patients who have undergone RYGB have altered PPI pharmacokinetics and compromised absorption mechanisms resulting from altered anatomy, rapid gut transit times and changes in the proximal gut hormonal and acidic milieu. As such, capsule breakdown in the reduced gastric pouch may be significantly impaired, limiting the effectiveness of "intact-capsule" PPIs (IC-PPI). More recently, "open-capsule" PPI (OC-PPI) therapy, which removes the enteric capsule leaving only the soluble medication to ingest, has gained interest. A recent retrospective study comparing OC-PPI vs IC-PPI therapy in MU healing after RYGB showed significant reduction in healing time (median time 91.0 days vs 342.0 days, respectively [$P < .001$]). They also report a lower number of endoscopic procedures and overall healthcare utilization in the OC-PPI group.[6] Other experts suggest commercially available preparation of nonenteric-coated omeprazole powder in sodium bicarbonate as the most appropriate formulation for patients who have RYGB anatomical change, however this remains understudied.[6]

In the absence of significant prospective evidence supporting any particular drug delivery system, the current standard of practice for treatment of MU after RYGB often remains similar to treatment of ulcerative disease in those without altered anatomy. In order to maximize the benefit of current medications, it is imperative that optimal drug delivery for the treatment of MU be further explored in a prospective trial. Furthermore, as the drug under study is already standard-of-care, there is no risk of inferior therapy. Depending on the finding, it may bring changes in current standard of practice.

1.2 Rationale

Retrospective data supports that OC-PPI improves healing of MU after gastric-bypass surgery compared to IC-PPI. No prospective or randomized controlled trial has been performed to assess this. Our study aims to compare if PPI taken as "open-capsule" improves healing of MUs post-gastric bypass surgery when compared to "intact-capsule" PPI.[6]

2 Study Objectives

2.1 Objective/Hypothesis:

We hypothesize that OC-PPI improves the time to healing of marginal ulcers after gastric bypass surgery compared to IC-PPI.

2.2 Aim (s)

1. To investigate if OC-PPI decreases the time of healing for marginal ulcers after gastric-bypass surgery as per endoscopic assessment per standard of care.
2. To investigate the number of EGD required after treatment with OC-PPI compared to IC-PPI following MU formation.
3. To investigate the difference in rate of complications and rate of treatment resistant ulcer.

2.3 Clinical Relevance/Impact

Results from this study could have an important impact on current management of MUs post-gastric bypass surgery, thereby reducing patient morbidity and healthcare utilization and improving overall outcomes following RYGB.

3 Subject Selection

3.1 Inclusion Criteria

Adult patients who have undergone RYGB with marginal ulcers found on upper endoscopy AND who are starting PPI medication (**as per standard of care for the treatment of marginal ulcers)**

3.2 Exclusion Criteria

Refusal to start PPI medication; Patients with current PPI use at the time of diagnosis.

4 Study Design

4.1 Study setting

We will perform a prospective single-blinded randomized control trial of patients diagnosed with marginal ulceration post-gastric bypass on upper endoscopy and undergoing standard of care treatment with PPI medication at the Cleveland Clinic from the date of approval of the IRB and forward. We will prospectively maintain the database in the RedCap platform and EPIC electronic medical records with the inclusion criteria as below.

Definitions:

- Marginal ulcers: Any ulcerations at the gastrojejunal anastomosis post-gastric bypass surgery that are seen on upper endoscopic assessment.
- OC-PPI: Open-capsule PPI, in which the enteric capsule is opened and the content medication is ingested alone
- IC-PPI: Intact-capsule PPI, in which the capsule is ingested as a whole
- Resolution of ulcer: Completely healed ulcer on endoscopic evaluation

Inclusion criteria:

- Subjects diagnosed with marginal ulceration post-gastric bypass on upper endoscopy.
    - Of note, the upper endoscopy is performed for any clinical indications at the discretion of the referring ordering provider.

Exclusion criteria:

- Refusal to start PPI medication OR current PPI use at the time of diagnosis of the marginal ulcer

4.2 Randomization Method and Blinding

- According to the current standard of care, all subjects will receive PPI medication. Subjects will be randomized to two arms: OC-PPI and IC-PPI. 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 1,3,5. Randomization will be carried out by having a piece of paper that has the number 1 or 2 (indicating each group) given to the NP to properly educate the patient. The treatment is going to be prescribed by the Nurse practitioner, so that endoscopist and data analysist are blinded from the treatment arm.

4.3 Follow-up and Data Collection

To ensure correct preparation of medication, subjects will be educated on medication administration while obtaining consent.

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).

Subjects will receive follow-up endoscopy at three-month intervals following initiation of intervention to monitor for healing of the ulcer, as per current standard of care. During every endoscopy visit and follow-up care visits per standard of care, patient's compliance with prescription will be documented. During endoscopy, data of pH of the gastric pouch will be collected as a secondary outcome. The gastric secretions at the pouch will be suctioned and tested for pH both by Litmus paper on the spot and confirmation by Cleveland Clinic Laboratory for pH, as a standard of practice. The endoscopy will be repeated at three months intervals until the healing of the ulcer is ensured.

Most ulcers heal with PPI, but there can be refractory ulcer as well. Interim analysis will be performed at 6 months and terminate the study if there is a significant difference in healing time. Also, if an ulcer remains after 1 year of therapy, these subjects will be deemed treatment-resistant and follow up will be terminated, at which point subjects will be offered the opportunity to cross-over or be treated with different medication at primary gastroenterologist's discretion. If, at any point, significant complications of ulceration occurs (including life-threatening bleeding, perforations, failure to thrive etc), appropriate care will not be delayed. Standard-of-care treatment such as surgical revision will not be withheld regardless of participation arms. These complications will also be tracked as a secondary end-point for the study.

4.4 End points

- Resolution of marginal ulceration post-gastric bypass as per upper endoscopy assessment. If the cross-over occurs during the trial, we will obtain time to resolution of cross-over group as follows:
  = (Date of cross-over) – (Date of resolution of marginal ulcer)
- Secondary:
  - Time to resolution of marginal ulceration as per documentation of upper endoscopy. This will be calculated in days as follow:
    = (Date of diagnosis of marginal ulcer) – (Date of resolution of marginal ulcer)
  - pH of Gastric pouch during each EGD

- Rates of severe complications (including life-threatening bleeding, perforations, failure to thrive) and rates of treatment-resistant ulcer

4.5 Recruitment of patients

Adult patients with history of RYGB referred to our Bariatric Endoscopy program for upper endoscopy procedure for any indication (at the discretion of the referring ordering provider) as per standards of care. Usual indications for upper endoscopy in post-gastric bypass surgery include (but not limited to): abdominal pain, anemia, nausea, vomiting, bloating, diarrhea, black stools, red stools, gastrointestinal bleeding, weight loss, weight gain, screening for Barrett's esophagus, pre-operatory anatomy assessment, gastroesophageal acid reflux disease (GERD), dysphagia, regurgitation.

The study will be specifically offered to patients when the ulcer is suspected and endoscopy is ordered by the provider, which will provide them enough time to think about the participation. The consent form will be provided via MyChart message right after pre-endoscopy instructions. Patients who are willing to participate will sign the consent form prior to the upper endoscopy in the pre-op area. The patient can also take a paper copy of the consent home. No phone calls or letters will be used for the recruitment plan. We will recruit 61 patients in each arm (total of 122 patients). Sample size calculation is detailed below.

4.6 PPI administration

Patients will be prescribed PPI per standard of care and the patient will pick it up from their preferred pharmacy as usual. Education material will be provided via MyChart with information on how to open the capsule. Prescription will specify how to take the medication according to randomization and the patient can follow directions based on education material (attached as separate file).

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.

5.2Sample size calculation

The sample size calculation was performed based on the primary outcome. Based on the Schulman's research,[7] "the median time to ulcer healing was 91.0 vs 342.0 days for the OC vs IC groups,

respectively (P < .001). By using a Cox proportional hazard model, patients in the OC group had a significantly decreased time to ulcer healing (hazard ratio, 6.04; 95% confidence interval, 3.74–9.06; P < .001) when compared with patients in the IC group", the median time-to-event in 2 groups and the hazard ratio was used in the sample size calculation.

The study plans 1 interim analysis and 1 final analysis. The planned follow-up time is 1 year. The loss-to-follow-up rate ranges from 40% to 50%. Based on the median time-to-event and hazard ratio, the hazard rates in 2 groups were calculated as h0=0.0020 and h1=0.0122. The loss hazard rate was calculated as 0.0019 (50%), 0.0016 (45%), and 0.0014 (40%).

$$S_j\left(t_j\right) = e^{-h_j t_j} = \frac{1}{2}$$

The sample size calculation with 2-stage group sequential design with 1 interim look was performed with significance level 0.05 and powers 80%. Analyses were performed using SAS (version 9.4; Cary, NC) software.

With 6.04 hazard ratio, the result of the sample size calculation shows that only 5 events need to be observed to conduct the interim analysis. While the small number from large effect size (large hazard ratio) may seem attractive, the distribution of 5 events in 2 groups can be problematic. One group may include less than 2 events due to random sampling, which makes it impossible to perform estimation during the analysis.

After collective discussion, the hazard ratio was changed to 2. By decreasing the effect size, the sample size will be increased, correspondingly, the power to detect the significance will increase.

Similarly, by using updated hazard ratios of 2, sample size calculation with group sequential design was conducted. However, another issue with it was arose. The number of patients needed during interim and during the final analysis are the same. In other words, recruitment (with an estimated 2-3 potential subjects enrolled per week) is quicker than the time-to-event, so, before the sufficient event number is observed for interim analysis, all patients have been recruited. Group sequential design with interim analysis was meant to save sample size by using multiple looks (interim analysis) during the follow-up. When the number needed during the interim analysis is the same as during the final analysis, there is no benefit from group sequential design, compared to fixed design.

Instead of conducting sample size calculation with group sequential design, fixed design, log-rank test was performed for sample size calculation. The sample size calculation with different proposed hazard ratio and loss-to-follow-up rate was performed with significance level 0.05 and powers 80%. Analyses were performed using SAS (version 9.4; Cary, NC) software.

In summary, with hazard ratio of 2 and loss-to-follow-up rate of 50%, sample size is calculated to be 122. Total accrual time will be 285 days and the total follow-up time is 650 days (285+365).

5.3 Interim analysis

We will conduct an interim analysis at 6 months after enrolling the first subject. If there is statistically significant difference in ulcer healing time, we will terminate the study and cross over IC-PPI group to OC-PPI. Should this happen, the team will continue to follow on the cross-over group to ensure ulcer healing time.

6 Safety and Adverse Events

Given that this study, which solely compares the method of administration of an FDA-approved medical treatment such as PPI medications for the treatment of marginal ulcers post-gastric bypass (as per standard of care), we do not anticipate any significant safety issues resulting from the study performance. However, the study staff will monitor any adverse events that occur among study performance. 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 the investigators listed on the IRB forms will have access to the Red Cap account, encrypted excel forms, and EPIC electronic medical record software containing the data. The Red Cap 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 Red Cap.

10 Key Words for PubMed

Peptic ulcer diseases, marginal ulceration, bariatric surgery, Roux-en-Y gastric bypass, bariatric endoscopy, proton pump inhibitor (PPI).

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