

Study Title: A Single-Center, Randomized, Prospective, Single-Blinded Study to Assess the Safety, Quality, and Tolerance of a Bowel Preparation Food Kit with Laxatives in a United States Veteran Population

Principal Investigator:

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I. Purpose:

The primary objective is to evaluate the safety, quality, and tolerance of a food kit with laxatives compared to the current practice of using split dose polyethylene glycol electrolyte solution (GoLYTELY) bowel preparation for colonoscopy.

Background:

Colorectal cancer (CRC) is the third most common cancer in the United States (1). Colonoscopy is the standard for CRC screening and surveillance (2). High quality bowel cleansing is essential to ensure adequate visualization and lesion detection (3,4). The bowel preparation should be acceptable, safe, convenient, tolerable, and inexpensive while reliably emptying the colon of fecal material without altering the colonic mucosa (5). In our experience, generally, less than 250 mL to 300 mL of water is used during a colonoscopy. Adequate hydration (6) and the combination of dietary restriction and oral cathartics have proven to be safe and effective for colonoscopy preparation (7).

There are several effective preparations for colonoscopy. However, adherence remains a concern. In our practice, patients frequently request an alternate bowel preparation due to taste, volume of preparation, or desire to eat solid food the day prior to the colonoscopy. There are ongoing efforts to improve the palatability and tolerability of colonoscopy bowel preparations. Recent studies have evaluated a low residue diet as an effective modality for bowel preparation with improved patient satisfaction (8,9,10,11). Therefore, we propose to evaluate the use of a food kit with intermittent laxative dosing as an effective bowel cleansing preparation while improving patient satisfaction and adherence.

II. Study Objectives:

1. To evaluate the safety, quality, and tolerance of a food kit with intermittent laxative dose regimen for colonoscopy bowel preparation
 - a. Safety
 - i. Safety assessments include adverse event monitoring by PI and study coordinator. Reporting of unexpected adverse events is described in Section VII, and events will be defined as below.
 1. Safety measures will be assessed as described in previous studies (9,11,12,13,14,15). These include abdominal pain, cramping, bloating, nausea, vomiting, headaches, weakness, hunger, and sleeping difficulties. These symptoms will be scored on a 5-point scale where 1 = "none," 2 = "mild," 3 = "bothersome," 4 = "distressing," and 5 = "severely distressing."

2. An adverse event will be a score of 5 of the above described symptoms or any observed or subject-reported adverse experiences.

b. Quality of bowel preparation

- i. Adequate bowel preparation will be defined using the Boston Bowel Preparation Scale score in the right, transverse, and left colon.
- ii. A score 0 to 3 will be assigned as below (16):

0 = Unprepared colon segment with mucosa not seen due to solid stool that cannot be cleared.

1 = Portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid.

2 = Minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well.

3 = Entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid.

- iii. A score ≥ 6 with each segment ≥ 2 should be achieved in $\geq 90\%$ to define as an adequate bowel preparation for colonoscopy (17)
- iv. From our baseline, the amount of water used during a colonoscopy will be categorized as, average is < 300 mL, moderate is 300 mL – 450 mL, copious is > 450 mL), and washing and suctioning time for stool remnants during the procedure will be recorded.
- v. The adenoma detection rate will be measured.

c. Tolerance

- i. Evaluate tolerance with a designed survey to be completed during the day of bowel cleansing prior to colonoscopy

III. Methods:

Study site: Central Virginia VA Medical Center

Study design: It is single-center randomized, prospective, single-blind study of subjects undergoing CRC screening colonoscopy. The anticipated end date is December 31, 2022.

Study funding: Happy Colon Foods will provide their food with laxatives kit at no cost.

Happy Colon Foods product: Food and laxative kit

Therapeutic area of interest: Bowel preparation quality, patient satisfaction including tolerability and palatability, and compliance

Study Population:

- Inclusion criteria:
 - Veterans undergoing index colonoscopy for colorectal cancer (CRC) screening
 - This includes a follow-up colonoscopy conducted after a positive non-invasive stool-based screening test (e.g., fecal immunohistochemical test) or direct visualization (e.g., CT colonography)
- Exclusion:
 - Personal history of colorectal cancer, inflammatory bowel disease, prior colon resection, antithrombotic therapy precluding polyp resection, biopsy proven Celiac disease, or had a prior colonoscopy

- Exclude those who had a prior colonoscopy to avoid cognitive bias including the misinformation effect.
- Inadequate examination due to inability to intubate the cecum or withdrawal time < 6 minutes
- Subjects with chronic kidney disease stage 3 or higher (an estimated glomerular filtration rate < 60 mL/min/1.73m² (18,19)) or age ≥ 70 years
 - Magnesium is excreted by the kidneys and this preparation should be avoided in patients with kidney disease or the elderly (20)
 - The use of magnesium adjunctively in combination with other laxatives is a well-tolerated preparation for colonoscopy (11,21,22)
 - In a retrospective review of 546 patients who received the food kit with laxatives by Happy Colon Foods appeared safe with no serious adverse events (11)
- Subjects hospitalized at the time of their scheduled procedure
- Control Group: Bowel cleansing for colonoscopy with the current regimen (instructional handout in supplement). This includes a clear liquid diet the day prior the scheduled procedure and a split dose regimen of 4 liters of polyethylene glycol 3350 (PEG-3350).
- Intervention Group: Bowel cleansing for colonoscopy with food and laxative kit, created by Happy Colon Foods, to begin the day prior to the scheduled procedure. The foods contain a low residue diet and intermittent dosing schedule of laxatives include PEG-3350 tasteless laxative powder, senna tablets, and a single dose of magnesium citrate (instructional handout in supplement).
- The anticipated enrollment period is May 15, 2022 to December 31, 2022.
- The study protocol will be approved by the IRB. Informed consent will be obtained from patients before any study-related procedures are initiated.
- Sample size consideration:
 - In a clinical prospective trial comparing a clear liquid diet with a fiber-free diet for colonoscopy preparation, the satisfactory bowel preparation was 81.4% in the fiber-free diet arm and 52.0% in the control group with a clear-liquid diet (9). Based on a significance level of 5% and power of 90%, to replicate these results we calculated that 49 patients would be needed in each group, i.e. - total sample size of 98 subjects (sealedenvelope.com/power/binary-superiority). Patient cancellations will be recorded. In our experience, the no show rate is 20%. Adjusting for the no-show rate, we will recruit 65 subjects in each study group totaling 130.

IV. Study Procedure and Data Collection:

- This is a prospective study at a single center at the Central Virginia VA Health Care Center. Referred patients will be seen in the outpatient gastroenterology clinic for CRC screening.
- Following informed consent, qualified candidates who elect to undergo colonoscopy for CRC screening and participate in the study will be randomized to either bowel preparation arm via a computer-based software (<https://www.randomizer.org/>).
 - Demographic data and clinical characteristics of included patients will be prospectively collected at the time of visit via interview and the electronic health record. This includes sex, race, body mass index, smoking status, medical history of diabetes, kidney disease, or chronic constipation using constipation-relation parameters such as, stool frequency per week and stool form, medications including use of opioids, calcium-channel blockers, or anticholinergics, prior abdominal or pelvic surgery, indication for colonoscopy, and history of colonoscopy.

- After randomization, the patient will be scheduled for a face to face visit with a study coordinator. Patient height and weight may be measured. The patient will receive the bowel preparation with oral and written instruction explaining the bowel preparation method (provided as supplements).
- The bowel preparation will begin at the standard time of 13:00 for the control group and 07:00 for the intervention group.
- Our staff will call the patient between 5 to 7 business days prior to their scheduled procedure date to review the bowel preparation instructions.
- To control for colonoscopy starting time, each enrolled patient will be scheduled with a 08:00 and 08:45 appointment.
- Immediately before colonoscopy, patients will complete a validated questionnaire (provided as supplement) addressing factors associated with the safety and tolerance of a bowel preparation (9,11,12,13,14,15,23,24).
 - Data related to the bowel preparation will be collected including ease of following instructional material, completion of preparation, time interval between the start of bowel preparation and the first defecation, adverse events including hunger, cramps, bloat, nausea, or insomnia, sleep quality the night before colonoscopy, and palatability and quantity of the laxative and food for those who received the food kits.
- A single blinded endoscopist will perform the colonoscopy. Procedure related parameters include cecal intubation rate, irrigation and suction time, amount of water used, withdrawal time, total procedure time, and Boston Bowel Preparation Scale (BBPS) score.
- Patient cancelations including reason, incomplete bowel preparation, or deviation from the instructions will be recorded.
- Histology reports will be reviewed to determine adenoma detection rate.

V. Data Analysis:

- Statistical Analysis:
 - Results for continuous variables will be expressed as medians and interquartile range for non-normally distributed data, or means and standard deviation for normally distributed data, which will be analyzed using Mann-Whitney U test or two sample unpaired t-test respectively.
 - These include 5-point scale for adverse events, BBPS score for quality of bowel preparation, palatability of the food provided in the kits, amount of water used during the procedure, irrigation and suctioning time, withdrawal time, and total procedure time.
 - Categorical variables will be expressed as percentages or frequencies and analyzed with chi-square test or Fisher's test. Results of univariate and multivariate analysis were expressed as odds ratio and 95% confidence interval. A two-sided P value < 0.05 will be statistically significant.
 - These include adenoma detection rate, patients' reported tolerance of the bowel preparation, and cancelation rate.
 - Variables associated with inadequate quality of bowel preparation (defined as BBPS < 2 in either segment) will undergo univariate analysis. Variables with P values < 0.1 will be assessed with multivariate analysis.
 - Propensity score matching for predictors of poor bowel preparation include higher body mass index (23), functional constipation (24,25,26), current smoker (27), diabetes, abdominopelvic surgeries, and opioid use (26).

VI. Study Limitations:

- Single-center and skewed patient demographic with a predominant male cohort
- Written instructions provided in a different format as the Happy Colon Foods food and laxative kit had written and visual instructions
- The laxative preparations have different start times, however, the intention is to adhere to the current standardized regimen.

VII. Ethical Considerations:

This study will be conducted according to good clinical practice guidelines, applicable laws and regulations.

VII. Data Safety Monitoring:

All data and safety monitoring will be performed by the PI of this study. Unanticipated problems related to will be reported to McGuire IRB within 5 days of study staff becoming aware. The purpose of the data is to conduct scientific research and no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. The principal investigator will be responsible to ensure the study is conducted in accordance with the protocol. The collection of personal patient information will be limited to the amount necessary to achieve the aims of the research. Only study personnel will collect data and enter a secure Excel database. Only de-identified data will be used for statistical analysis. The protocol will be submitted to the IRB for review and approval.

Potential risks and Unanticipated Problems: As with any available bowel prep regimen, potential risks include intolerance with the bowel cleansing regimen and symptoms such as abdominal pain, cramping, bloating, nausea, vomiting, headaches, weakness, hunger, and sleeping difficulties, or incomplete bowel examination. There is always the small risk of breach of confidentiality. The confidentiality of data will be protected by assigning a code to each subject's data. Investigator will securely maintain the key to the code in locked cabinets in locked offices, or within password-protected VA environment. Key will not leave the VA. Study data will be maintained behind VA firewalls on VA computers which are password protected, and study data may be accessed only by study personnel listed on the Study Personnel List.

Benefits to subjects: Improve patient compliance and tolerance of bowel preparations for colonoscopy while maintaining a quality examination.

Costs to subjects: None.

Compensation to subjects: None.

Conflicts of Interest: No conflicts of interest have been reported.

Relevant Financial Disclosures: Happy Colon Foods provided their food and laxative kits.

Grant Support: None

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