RANDOMIZED COMPARISON OF THE IMPACT OF SODIUM PICOSULFATE, MAGNESIUM OXIDE AND ANHYDROUS CITRIC ACID VERSUS POLYETHYLENE GLYCOL BOWEL PREPARATION ON INPATIENT COLONOSCOPY QUALITY PARAMETERS

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INTRODUCTION & BACKGROUND:

Effective bowel cleansing is paramount for adequate visualization of the colonic mucosa. Inadequate bowel preparation is reported in as high as 20-30 %[1] of all outpatient procedures but it is higher in hospitalized patients with rates up to 50 % being reported[2]. Hospitalization is associated with a risk of poor bowel cleansing[3] and leads to a prolonged length of stay and increased costs in these patients[4]. Improvement in bowel preparation quality of hospitalized patients has shown to decrease the length of stay and save more than $418,200 annually at a tertiary care hospital[5].

Patient tolerability of the bowel preparation agent may be an important factor affecting the quality of colon cleansing[6]. Large volume (4-liter) polyethylene glycol electrolyte solution (PEG-ELS) bowel preparation is safe and effective[7], yet poor patient tolerability secondary to the large volume that needs to be ingested remains it's Achilles' heel[8,9]. Several, small volume (2-liter) bowel preparation agents are available to counteract this problem. Sodium picosulfate, a stimulant laxative, magnesium oxide, and anhydrous citric acid (SP/MC) preparation is a 10-ounce bowel preparation which has demonstrated comparable efficacy, better tolerability and a lower incidence of adverse events than both 2-liter and 4-liter polyethylene glycol based bowel preparations[10-15]. In addition to the volume related improvement in tolerability and adverse

events with SP/MC versus other FDA approved bowel preparations, strong evidence shows that ingesting at least half of the bowel preparation on the day of the colonoscopy, called split dosing, rather than a single day before dose administered the evening before the examination, not only maximizes the cleansing efficacy but also improves tolerability as well[16,17].

IMPACT:

There are no studies comparing the efficacy and tolerability of small volume versus large volume bowel preparations in hospitalized patients. Furthermore, even though the use of split dosing has demonstrated higher efficacy and improved tolerability in outpatients[18], there is no literature assessing the impact of split versus single dosing on the quality of bowel preparation in hospitalized patient undergoing colonoscopies. Our study aims to provide data to demonstrate that inpatients experience the same benefit of SP/MC and split dosing as has been noted in outpatients.

HYPOTHESIS:

1) SP/MC (sodium picosulfate, magnesium oxide, and anhydrous citric acid) bowel preparation will increase the proportion of inpatients with adequate bowel cleansing compared to 4-liter PEG-ELS bowel preparation. Split dose bowel regimens of 4-liter PEG-ELS and SP/MC will increase the proportion of inpatients with adequate bowel cleansing compared to a single, day before dose of 4-liter PEG-ELS and SP/MC.

PRIMARY OUTCOMES:

The primary end-point of this study will be the percentage of in-patients with "satisfactory" bowel cleansing. The efficacy of bowel cleansing will be measured using the Boston Bowel Preparation Scale (BBPS) [19, 20]. The BBPS divides the colon into three segments (right, transverse and left) which are scored from 0 to 3 (0= colonic mucosa not seen due to solid stool that cannot be cleared, 1 = only a portion of mucosa of the colon segment is 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 is seen well and 3 = entire mucosa of colon segment is seen well with no residual staining, small fragments of stool or opaque liquid).

A total BBPS score ≥ 6 AND ≥ 2 in all segments of the colon will be defined as a "satisfactory bowel preparation". BBPS scores of < 6 OR < 2 in any segment of the colon will be taken as "unsatisfactory cleansing in the final analysis".

SECONDARY OUTCOMES:

Secondary outcomes that will be measured are 1) tolerability of the bowel preparation assessed by a patient survey using a modified 5-point Likert scale, 2) percentage of patients requiring a repeat procedure due to unsatisfactory bowel preparation, and 3) percentage of patients receiving rescue medications including magnesium citrate or fleets enemas.

METHODOLOGY:

STUDY DESIGN:

A randomized, single-center, assessor-blinded trial will be conducted at Cleveland Clinic, a tertiary healthcare center in Ohio, United States. Eligible inpatients at the Cleveland Clinic scheduled for colonoscopy under conscious sedation or general anesthesia will be invited to participate.

Patients eligible for conscious sedation will be randomized at a 1:1:1:1 ratio to receive 1 of the 4 proposed bowel preparation regimens using block randomization. This will be done with a computer-aided system prior to study commencement. The four groups are as follows:

- Group A: 4 Liter PEG-ELS administered as a single day before dose the evening before the colonoscopy,
- Group B: 4 Liter PEG-ELS administered as a split dose the evening before and 4 hours prior to the colonoscopy (currently the standard to which other bowel regimens are compared[21]),
- Group C: SP/MC administered as a single day before dose the afternoon or early evening before the colonoscopy,
- Group D: SP/MC administered as a split dose the afternoon or early evening day before and 4 hours prior to the colonoscopy.

Patients who require general anesthesia will be randomized at a 1:1 ratio to the single, 'day before dose' only groups for both PEG-ELS and SP/MC since the anesthesia protocol at our institution mandates strict enforcement of nothing per oral after midnight on the day of the procedure.

- Group E: 4 Liter PEG-ELS administered as a single day before dose the afternoon or early evening before the colonoscopy,
- Group F: SP/MC administered as a single day before dose the afternoon or early evening before the colonoscopy,

- All procedures will be done at the endoscopy suite on the main campus at Cleveland Clinic by a board certified gastroenterologist. The physician and the patients will not be blinded due to major differences in the volume and timing of the bowel cleansing regimens. Primary end-points of this study will be measured between the participants in the all 6groups.

INCLUSION/EXCLUSION CRITERIA:

All eligible inpatients at Cleveland Clinic older than 18 years of age scheduled for a colonoscopy will be invited to participate in our study. Patients will be excluded if they have/are:

1) Creatinine clearance less than 30 ml/min,
2) History of heart failure with current shortness of breath at rest causing limited physical activity, arrhythmia, unstable angina ,or acute myocardial infarction,
3) Small bowel obstruction, ileus or bowel perforation
4) Dementia or cognitive dysfunction to an extent that they cannot perform the study related documentation or consent to participate in the study,
5) Gastroparesis,
6) Toxic megacolon or undergoing colonoscopy for decompression,
7) Taking oral tetracyclines, fluoroquinolones, antibiotics, iron, digoxin, chlorpromazine and penicillamine within 2 hours before or less than 6 hours after administration of CLENPIQ, or stimulant laxatives within 24 hours,
8) Allergy to any of the ingredients in CLENPIQ or golytely and/or
9) If the procedure is planned in the intensive care unit (ICU).

A member of the study team will identify hospitalized patients who have a colonoscopy procedure scheduled within the next 48 hours. A member of the study team will review the patient's electronic medical record to ensure that the patient is eligible to participate in the study.

PATIENT EDUCATION:

There is an educational initiative currently underway at Cleveland Clinic to improve the inpatient colonoscopy experience which will also be applicable to all the patients enrolled in our study. The initiative entails:

1) Educating the nurses (via educational posters and small didactic sessions),

2) Educating the internal medicine and surgery residents who order the bulk of the inpatient colonoscopies (via educational posters and small didactic sessions),

3) Educating the patients (via detailed instructional pamphlets which will be distributed on the day before the colonoscopy)

Every patient who consents for inclusion in our study will also receive written instructions educating them about the appropriate preparation that needs to be undertaken to make their colonoscopy successful, with special emphasis on proper technique of the bowel cleansing process. Additionally, an investigator or study coordinator would be available to answer any questions that the patient might have related to the bowel purgatory process or the procedure itself.

A clear liquid diet is preferred after awakening the entire day before the procedure. Patients will not be excluded from participating in the study if they have eaten solid food the day before the procedure. Patients will be instructed to consume clear liquids (no solid food) once they begun consuming the bowel preparation until after their colonoscopy. To ensure better comprehension of the patient and success of the bowel cleansing process, the written instructions will specify drinks that qualify as clear liquids. The patient's in each group will be instructed to consume the bowel preparation agent as per their approved FDA labels. Administration of bowel preparations as a split dose is currently the recommendation of choice, for colonic cleansing prior to colonoscopy, in national guidelines (including American Society of Gastrointestinal Endoscopy[16], American College of Gastroenterology[23] and United States Multi-Society Task Force for colorectal cancer screening[17]).

1) <u>4 LITER PEG-ELS GROUP (CONSCIOUS SEDATION/SINGLE DOSE DAY BEFORE):</u>

Group A will be instructed to drink the 4-liter PEG-ELS at rates of 8 ounces (240 ml) every 10 min the evening before their colonoscopy and finish drinking the bowel preparation in three hours. They may continue to drink additional clear liquids until 2 hours before their colonoscopy.

2) <u>4 LITER PEG-ELS GROUP (CONSCIOUS SEDATION/SPLIT DOSE):</u>

Group B will be instructed to complete their bowel preparation in two steps for split dosing regimen. They will begin drinking an 8-ounce glass of bowel preparation every 10 minutes for a total of 8 glasses (~ 2 liters) the evening before the colonoscopy and finish drinking the bowel preparation in 1.5 hours . They may continue to drink additional clear liquids. This dosing scheme will then be repeated 4 hours before the scheduled time of their colonoscopy where they will drink an 8-ounce glass of PEG-ELS every 10

minutes for a total of 8 glasses (~2 liters) and finish drinking the bowel preparation in 1.5 hours. They may continue drinking additional clear liquids until 2 hours before their colonoscopy.

3) SP/MC GROUP (CONSCIOUS SEDATION/SINGLE DOSE DAY BEFORE):

Group C will be instructed to drink sodium picosulfate, magnesium oxide and anhydrous citric acid (CLENPIQ) which is ready to drink and does not need to be diluted. Patients will consume the first bottle of SP/MC the afternoon or evening before their colonoscopy followed by at least five (5) 8-ounce glasses of clear liquids consumed at their own pace, within the next 5 hours. The patient will consume the second bottle of SP/MC 5 hours after beginning the first bottle followed by at least 3 8-ounce glasses of clear liquids within the next 2 hours.. They may continue to drink additional clear liquids until 2 hours before their colonoscopy.

4) SP/MC GROUP (CONSCIOUS SEDATION/SPLIT DOSE):

Group D will be instructed to drink sodium picosulfate, magnesium oxide and anhydrous citric acid (CLENPIQ) which is ready to drink and does not need to be diluted. . Patients will complete their bowel preparation in two steps for the split dosing regimen. Patients will consume the first bottle of SP/MC the afternoon or evening before their colonoscopy followed by at least five (5) 8-ounce glasses of clear liquids consumed at their own pace, within the next 5 hours. Patients may continue drinking additional clear liquids**.** This dosing scheme will then be repeated 4 hours prior to their colonoscopy. Patients will consume the second bottle of SP/MC followed by at least 3, 8 ounce glasses of clear liquids over the next two hours. . They may continue drinking additional clear liquids until 2 hours before their colonoscopy.

5) 4 LITER PEG-ELS GROUP (GENERAL ANESTHESI/SINGLE DOSE DAY BEFORE):

Group E will be instructed to drink the 4-liter PEG-ELS at rates of 8 ounces (240 ml) every 10 min the afternnoon or evening before their colonoscopy and finish drinking the bowel preparation within 3 hours and no later than midnight . They may continue to drink additional clear liquids until midnight and then nothing to eat or drink until after their colonoscopy.

6) SP/MC GROUP (GENERAL ANESTHESIA/SINGLE DOSE DAY BEFORE):

Group F will be instructed to drink sodium picosulfate, magnesium oxide and anhydrous citric acid (CLENPIQ) which is ready to drink and does not need to be diluted. Patients will consume the first bottle of SP/MC the afternoon or evening before their colonoscopy followed by at least five (5) 8-

ounce glasses of clear liquid consumed at their own pace, within the next 5 hours. The patient will consume the second bottle of SP/MC 5 hours after beginning the first bottle followed by at least 3 glasses of 8-ounce clear liquids which must be completed by midnight the day before the procedure. They may continue to drink additional clear liquids until midnight and then nothing to eat or drink until after their colonoscopy.

ASSESSMENT OF PATIENT TOLERABILITY AND ADVERSE EFFECTS:

Each patient will be provided a survey at the time of enrollment. The patients will be instructed to complete the survey in "real time" (as they are drinking the preparation). The co-investigator or the study coordinator will collect the survey from the patient prior to receiving sedation for their colonoscopy procedure. The co-investigator or study coordinator will review the survey to ensure all questions are answered.

The purpose of the survey will be to document the following information:

a. Demographic details (including level of education and annual income),

b. The start time and end time of the ingestion of bowel cleansing agent,

c. Total amount of the cleansing agent ingested (to be recorded using a visual depiction of the remaining bowel preparation agent in the container),

d. Full dose of the bowel cleanser ingested (yes versus no),

e. Details including the type and timing of symptoms encountered (nausea, vomiting, abdominal pain, bloating, thirst, dizziness, headache or paresthesia),

f. If any of the above-mentioned symptoms were present prior to the start of the cleansing process, did the use of the purgative agent make them worse (yes versus no),

g. Ease of use based on a modified 5-point Likert scale[25]: "very easy," "easy," "tolerable," "difficult," or "very difficult" (score 5–1, respectively),

h. Palatability based on a modified 5-point Likert scale: "very good," "good," "fair," "bad," or "worst" (score 5–1, respectively), – *Patients who score ≥3 points in items h) and i) will be classified as the tolerant group.*

i. Willingness to use the same agent again (yes versus no),

SAMPLE SIZE CALCULATION:

Preliminary data has been gathered over the last one year at Cleveland Clinic which has shown adequate bowel preparation rates (as defined by the reported preparation quality of good or excellent on the Aronchik scale) in about 46 % of all hospitalized patients undergoing colonoscopy. Due to the educational initiative currently underway at our institution, we will assume that the rates of adequate bowel preparation will be 50 % (which will be taken as the rate of adequate preparation in our control arm of the 4 L PEG-ELS). To demonstrate a 10 % increase in rates of adequate cleansing with the use of P/MC at a confidence level of 95% and a power of 85 %, a sample size of at least 886 subjects would be required. Countering for a possible difference that may exist between our estimated and existing rates of satisfactory bowel preparation, we will increase the sample size by at least 10 % for a total of 1000 patients (250 patients per group).

FEASIBILITY:

A total of 1145 inpatient colonoscopies were done at Cleveland Clinic from April 2018 to April 2019, averaging 190 colonoscopies per month. Assuming a recruitment rate of 75 %, 12 months of recruitment will be needed to obtain a sample size of 1000 patients (250 per group) and complete our study.

BOWEL PREPARATION AGENTS:

CLENPIQ (SP/MC):

INDICATIONS/CONTRAINDICATIONS:

The use of CLENPIQ will be studied in our project and compared to the standard of care which is golytely (4 L PEG-ELS). CLENPIQ is a combination of sodium picosulfate, a stimulant laxative, and magnesium oxide and anhydrous citric acid (SP/MC) which form magnesium citrate, an osmotic laxative, indicated for cleansing of the colon as a preparation for colonoscopy in adults. Contraindications to CLENPIQ use include 1) patients with severely reduced renal function (creatinine clearance less than 30 mL/minute) which may result in accumulation of magnesium, 2) gastrointestinal obstruction or ileus, 3) bowel perforation, 4) toxic colitis or toxic megacolon, 5) gastric retention, and 6) an allergy to any of the ingredients in CLENPIQ.

ADVERSE EFFECTS:

The safety and efficacy of CLENPIQ has been established based on adequate and well-controlled studies of another formulation of sodium picosulfate, magnesium oxide and anhydrous citric acid.

DRUG INTERACTIONS:

Use caution when prescribing CLENPIQ for patients with conditions or who are taking medications that increase the risk for fluid and electrolyte disturbances or may increase the risk of renal impairment, seizure, arrhythmias, and prolonged QT in the setting of fluid and electrolyte abnormalities. This includes patients receiving drugs which may be associated with hypokalemia (such as diuretics or corticosteroids, or drugs where hypokalemia is a particular risk, such as cardiac glycosides) or hyponatremia. Use of caution is also advised when CLENPIQ is used in patients with severe active colitis, on nonsteroidal anti-inflammatory drugs (NSAIDS) or drugs known to induce Antidiuretic Hormone Secretion (SIADH), such as tricyclic antidepressants, selective serotonin re-uptake inhibitors, antipsychotic drugs and carbamazepine, as these drugs may increase the risk of water retention and/or electrolyte imbalance.

It is important to note that oral medications administered within one hour of the start of administration of CLENPIQ solution may be flushed from the GI tract and the medication may not be absorbed. Tetracycline and fluoroquinolone antibiotics, iron, digoxin, chlorpromazine, and penicillamine, should be taken at least 2 hours before and not less than 6 hours after administration of CLENPIQ to avoid chelation with magnesium. Prior or concomitant use of antibiotics with CLENPIQ may reduce the efficacy of CLENPIQ as conversion of sodium picosulfate to its active metabolite BHPM is mediated by colonic bacteria.

GOLYTELY (4-LITER PEG-ELS):

INDICATIONS/CONTRAINDICATIONS:

GOLYTELY is indicated for bowel cleansing prior to colonoscopy and barium enema X-ray examination in adults. It is contraindicated in patients with gastrointestinal (GI) obstruction, ileus, or gastric retention, bowel perforation, toxic colitis or toxic megacolon or known allergy or hypersensitivity to any component of golytely.

ADVERSE EFFECTS:

Nausea, abdominal fullness and bloating are the most common adverse reactions (occurred in up to 50% of patients) to the administration of golytely. Abdominal cramps, vomiting and anal irritation occurs less frequently. These adverse reactions are transient and usually subside rapidly. Cases of urticaria, rhinorrhea, dermatitis and (rarely) anaphylactic reaction have been reported which may represent allergic reactions.

Published literature also contains isolated reports of serious adverse reactions following the administration of PEG-electrolyte solution products in patients over 60 years of age which include upper GI bleeding from Mallory-Weiss Tear, esophageal perforation, asystole, sudden dyspnea with pulmonary edema, and "butterfly-like" infiltrates on chest X-ray after vomiting and aspirating PEG.

DRUG INTERACTIONS:

Use of caution is advised when prescribing golytely for patients who are using medications that increase the risk for fluid and electrolyte disturbances or may increase the risk of seizures, arrhythmias, and prolonged QT in the setting of fluid and electrolyte abnormalities. Oral medication administered within one hour of the start of administration of golytely may be flushed from the gastrointestinal tract and the medication may not be absorbed properly. Concurrent use of stimulant laxatives like bisacodyl or sodium picosulfate with golytely may increase the risk of mucosal ulceration or ischemic colitis and will be avoided.

STATISTICAL ANALYSIS:

Descriptive data will be presented for all 4 groups; these include means ± standard deviations, median [25^{th}, 75^{th} percentiles] or frequency (percent). Regression analysis will be used to assess the primary and secondary outcomes of interest; logistic regression will be used to model satisfactory bowel preparation and need of repeat procedure while proportional odds logistic regression will be used to model tolerability. For each model, the outcome of interest will be modeled as the dependent variable with the type of bowel preparation (PEG-ELS vs. SP/MC) and type of dose (single vs. split) as the independent variables; the interaction between these two will be tested and included in the models if $p<010$. SAS (version 9.4, The SAS Institute, Cary, NC) will be used for all analyses and a $p < 0.05$ will be considered statistically significant.

VARIABLES TO BE STUDIED:

- Basic demographics: Age, sex, ethnicity, income status, BMI, educational level.
- Pertinent medical history: Comorbidities including history of diabetes, stroke, Parkinson's disease, hypertension, thyroid disease, constipation, ASA class, opiate use, TCA use, history of IBD, poor preparation in previous colonoscopies (yes/no), Charleston comorbidity index, use of anti-emetics for the bowel cleansing (yes/no).

- Procedure details: Date, indication, bowel preparation quality (reported as BPPS), type of sedation, start time of the procedure, the end time of the procedure, cecal intubation (yes/no), cecal intubation time and withdrawal time.

DATA MANAGEMENT:

- Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (P/MCS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes Cleveland Clinic and was initiated at Vanderbilt University. The database is hosted at the Cleveland Clinic Datacenter. The system is protected behind a login and Secure Sockets Layer (SSL) encryption. There is an audit trail tracking all logins and activities in the database. Data collection is customized for each study or clinical trial based on a study-specific data dictionary defined by the research team with guidance from the REDCap administrator in Quantitative Health Sciences at the Cleveland Clinic.
- Any unintended data breaches will be immediately reported to the institutional IRB. Data analysis will be performed by a member of the Department of Quantitative Health Sciences, Lerner Research Institute.
- In this study, no elements have been identified with foreseeable risks to participants. A list of randomly generated participant numbers will be utilized for all patient identification, data collection and data analysis by the research team. Patients' data will be identified by these numbers when key study personnel work with the data. The list linking participant numbers to patient medical record numbers will be stored in a secure, locked environment and will only be utilized to re-verify data. The study will utilize de-identified data for data analysis and reporting.
- Participants will be recruited for this study and will have to be able to provide consent for the colonoscopy procedure and for inclusion in the trial. All participants will also have to agree to complete the survey. Data will be collected from institutional EMR (EPIC) for details on patients' demographics, laboratory results, and procedure details. This is related to customary clinical duties carried out by residents, fellows, and staff during the course of their education and employment at Cleveland Clinic.

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