L-Menthol Injection as a Novel Technique During Colonoscopy:

The MINT-C Study

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Primary Objectives:
1. Evaluate for changes in adenoma detection rates with the use of intraluminal peppermint oil application vs sterile water application during colonoscopy.

Secondary Objectives (non co-primary; non-key secondary end points):
1. Evaluate for changes in Polyp detection rates
2. Evaluate for changes in total procedure time, cecal intubation time, and withdrawal time with the use of intraluminal peppermint oil application vs placebo during colonoscopy.
3. Evaluate for changes in advanced adenoma detection rates with the use of intraluminal peppermint oil application vs placebo during colonoscopy. Advanced adenoma will be defined as an adenoma with significant villous features (>25%), size of 1.0 cm or more, high-grade dysplasia, or early invasive cancer.
4. Evaluate for changes in cancer detection rates with the use of intraluminal peppermint oil application vs placebo during colonoscopy.
5. Evaluate for changes in reported patient comfort levels with the use of intraluminal peppermint oil application vs placebo during colonoscopy.

Methodology:
The institutional investigational pharmacy at each site will create and dispense a 1 liter solution containing 1.6% peppermint oil (solution A) or placebo (solution B). Once a patient consents for the procedure and is brought to the endoscopy room, research personel will selecte an opaque envelope that is serially numbered, labeled, and randomly assigned in a variable block fashion with a 1:1 ratio in blocks of 4 or 6 stratified by institution and indication for procedure (surveillance or screening). This contents of envelope will contain a paper assigning the patient to the either solution A or solution B. The research personal will draw up 20mL of this solution in each of 4 total plastic syringes. These syringes will be placed on the endoscopy cart to be used by the endoscopist during the procedure as described in the paragraphs below. Each site will also utilize an essential oil diffusing device in the endoscopy suite to mask any smells that could potentially confound blinding.

<u>Solution A) Peppermint oil solution (1.6% peppermint oil, which is 0.8% L-menthol)</u>

Ingredients:
1) 16mL of peppermint oil (provided by the NowFoods® company)
2) 0.4mL of Tween® 80 (i.e. Polysorbate 80) – this is a commonly used food additive that acts as a surfactant to bring the peppermint oil into solution
3) 1L prepackage sterile water
4) 2.6mL of undyed simethicone

Instructions to prepare:
1) Add peppermint oil, tween, and simethicone to sterile water. Then, shake vigorously.
2) Once solution has settled, and patient has been randomized, draw 20mL of solution into a plastic syringe
3) As a result, in our each syringe will contain **<u>160mg of L-Menthol.</u>**

<u>Solution B) Placebo solution</u>

Ingredients:

1) 0.4mL of Tween® 80 (i.e. Polysorbate 80) – this is a commonly used food additive that acts as a surfactant to bring the peppermint oil into solution
2) 1L prepackage sterile water
3) 2.6mL of undyed simethicone

Instructions to prepare:

4) Add tween and simethicone to sterile water. Then, shake vigorously.
5) Once solution has settled, and patient has been randomized, draw 20mL of solution into a plastic syringe

In the morning of the procedure, patients undergoing screening and surveillance colonoscopy will be pre-screened to evaluate if they meet inclusion criteria. Once patients are identified they will be approached by study personnel (consisting of PI, co-investigators, and additional staff supervised by the PI or co-investigators) to determine their willingness to participate in the study. If the subject is willing to participated, he or she will undergo written consent for participation in the study by research protocol personnel. Patients will be questioned regarding their allergy status specific to peppermint oil and this will be documented in the consent form and in the REDCap database.

Once the patient is willing to participate and inclusion/exclusion criteria are met based on pre-screening in the EMR, which includes evaluation of prior baseline labs, designated research personnel (that will not be involved in the actual colonoscopy) will draw up 20mL of solution in each of 4 total plastic syringes. Placebo and experimental solutions will be similar in appearance. These syringes will be placed on the endoscopy cart to be used by the endoscopist during the procedure as described in the paragraphs below.

Endoscopy rooms being used for this study will use an essential oil diffuser to add olfactory blidning. As the experimental solution has a distinct odor of peppermint oil, the diffusing device will prevent olfactory detection by the endoscopist and staff.

Endoscopists and trainees working with supervising endoscopists will be provided with a total of four (4) 20mL prefilled syringes consisting of either solution A (1.6% peppermint oil, which is 0.8% L-menthol) or solution B (protocol). Both solutions are similar in appearance.

Endoscopists will be required to deliver 1 syringe at the cecum and 1 syringe in the sigmoid colon. Up to 2 additional doses can be delivered at the discretion of the endoscopist up to a maximum of 4 total doses (**max total dose = 640mg L-Menthol**).

After the procedure, endoscopists will be provided with a survey which will ask them to identify in which arm of the trial they participated. Additionally patients will be provided a survey at the end of the procedure to rate their pain and discomfort during the procedure. Both surveys are available for review at the end of this protocol.

ADR, PDR, total procedure time, cecal intubation time, withdrawal time, advanced adenoma detection rates, and cancer detection rates will be calculated and compared between both groups. Statistical analysis methods are described below.

Patients will be followed up by telephone as described in the section below titled, "Follow up after completion of procedure".

Type of Blinding: Fully masked through the use of identical appearing solutions and additional measures to maintain blinding, such as using an essential oil diffuser to create a peppermint oil smell in the room to prevent olfactory detection of peppermint oil. In addition, effectiveness of

blinding will be assessed by providing the endoscopist with a survey asking him or her to guess which group to which their patient belonged. Also, blinded adjudication of key outcomes, such as adverse events leading to premature discontinuation of the procedure will be carried out.

Allocation concealment: serially numbered, opaque, sealed envelopes; variable block randomization

Sample Size (Including Ratio of Subjects Assigned to Treatments)/Power: This study is projected to enroll a total of 300 subjects (150:150) in group 1 and 2 respectively.
Given a power of 80% and a confident level of 95% with a p-value of 0.05, to determine a 20% difference in ADR between both groups, a sample size of 274 is required. Accounting for poor preps or withdrawal of consent, an increase in the sample size to 300 is projected.

Randomization: Subjects will be randomized in the two treatment arms in a 1:1 ratio. Randomization will be based on a computer-generated random code schedule and will occur immediately prior to beginning the procedure so as to keep drop out rate to a minimum.

Stratification: Eligible patients will stratified into 2 groups, those undergoing primary screening colonoscopies and those undergoing surveillance colonoscopies. They will also be stratified by institution.

Diagnosis and Criteria for Inclusion: Adult subjects who are undergoing screening or surveillance colonoscopies.

Facilities Description and Patient Population: This study will be carried out in two separate facilities in order to capture a broad patient population base with various rates of baseline ADRs. The first is a large-tertiary referral care center that performs over 5000 diagnostic and screening colonoscopies per year. The second institution is a large Veterans Affairs Medical Center that also performs over 3500 colonoscopies per year.

The subject must meet ALL criteria listed below for entry:

Inclusion Criteria:
1. At least 50 years of age in Caucasians or 45 years of age in African-Americans.
2. Patients undergoing primary screening colonoscopy (either average risk or increased-risk) or surveillance colonoscopy after prior screening/surveillance colonoscopy.
3. Capable of understanding instructions, adhering to study schedules and requirements, and willing to provide informed consent.

Exclusion Criteria:
1. History of colectomy, partial or complete
2. Symptoms suggesting possible colorectal stenosis or cancer
3. Inflammatory bowel disease
4. Familial polyposis syndromes
5. History of, or current diagnosis of colorectal cancer
6. American Society of Anesthesia Physical Stats (ASA PS) score of IV or greater
7. Non-correctable coagulopathy
8. Currently receiving anti-thrombotic therapy, with an INR > 1.5
9. Poor prep, total BBPS score < 6, or any part of the colon < 2.
10. Patients with known allergy to peppermint oil or peppermint containing products.
11. Patients taking calcium channel blockers (Amlodipine, Nifedipine, Verapamil, Diltiazem, Dihydropyridine, Felodipine, etc).

Product, Dose, Mode of Administration: Peppermint oil solution will be prepared as described above in 20mL aliquots of 1.6% peppermint oil. A total of 4 separate 20mL aliquots will be provided in standard plastic syringes for patient who are randomized to the experimental arm of the trial. The placebo solution will be provided in the same fashion in 4 separate 20mL aliquots provided to those randomized to the placebo arm of the trial. The endoscopist will be required to inject the contents of the provided syringes through the endoscope at specific times during the procedure. The first dose will be delivered during the withdrawal portion of the exam in the cecum. After this the endoscopist should proceed with the exam as per standard procedure. A second dose will be delivered in proximal portion of the sigmoid colon. Up to two additional doses can be delivered at any time during the procedure as per the judgment of the endoscopist. Importantly, after injecting the 20mL of solution through the endoscope, the physician will also inject an additional 20mL air through the endoscope to ensure the complete dose was delivered. The endoscopists will note where all doses were delivered in the post procedure survey.

The dosing below and the protocol above has been approved by the FDA IND committee:

Each 20mL aliquot of experimental solution contains: 160mg L-Menthol (320mg Peppermint oil) The maximum delivered dose is 4 separate 20mL aliquots: 640mg L-menthol (1280mg peppermint oil).

The peppermint oil to be used in this study is produced by Now Foods® and purity data and manufacturing data has been provided to the FDA and this is part of the attached FDA IND application. As per the FDA IND committee recommendations, for the proposed trial, the pulegone (an agent shown to be hepatoxtic in animal studies) content of the clinical batch of peppermint oil to be used in the study must be known. As per the European recommendation for peppermint oil used in herbal medicine products, the batch must contain no more than 2.5% of pulegone. The official certificate of analysis showing the pulegone content for the batch of peppermint oil to be used during the study will be provided to the respective IRBs and the FDA, if needed.

Additional Therapy, Dose, Mode of Administration: ANY approved bowel prep, such as GoLYTELY® (Polyethylene glycol-3350 236 g, sodium sulfate 22.74 g, sodium bicarbonate 6.74 g, sodium chloride 5.86 g, and potassium chloride 2.97 g) 4 liters given orally the night before colonoscopy as bowel preparation or MoviPrep® (Polyethylene glycol-3350 100 g, sodium sulfate 7.5 g, sodium chloride 2.691 g, potassium chloride 1.015 g, sodium ascorbate 5.9 g, and ascorbic acid 4.7 g). Split-preps and extended-preps will be encouraged as per hospital protocol and clinical indication. Conscious sedation according to hospital protocol will be provided during colonoscopies as per standard practice.

Duration of Treatment:
Group 1 - Peppermint oil will be applied intraluminally during time taken for colonoscopy only.
Group 2 – Placebo solution will be applied intraluminally during time taken for colonoscopy only.

Criteria for Evaluation:
Safety assessments will be conducted at start and finish of colonoscopy. Patients will have blood tests reviewed in the electronic medical records system and undergo standard pre-endoscopy history and physical examinations. ADRs will be calculated after colonoscopies are completed. Total time spent in colonoscopy including withdrawal time (defined as time taken to withdraw endoscope from cecum to the end of the patient's GI tract) will be recorded. The bowel-prep will be graded according to Boston bowel prep score (BPPS) and recorded for each patient.

Risks and discomforts and how minimized:

1) Breech of privacy - The data, while securely stored, has a small risk to be breeched and is a risk to participating in this study.
2) There is a small risk of allergy to peppermint oil, and, if encountered, we will treat accordingly to standard care protocol.

The following steps will be taken to minimize these risks are:
1) Risks of confidentiality breech will be minimized using security features as previously defined including use of a secure, online database application (REDCap) and storage of hard-copy documents in a locked cabinet in the PI's locked office.
2) Risk of allergy to peppermint oil will be minimized by asking subjects prior to the procedure for known allergies to peppermint or its byproducts.

Benefits to subjects

Currently, there are no known benefits for subjects who participate in this study.

Costs to the subject

There will be no cost to the subject for participation this study.

Alternative(s) to participation

The patient can choose not to participate in the study and proceed with standard colonoscopy as per routine protocol.

Payment to the subjects (include both reimbursement and incentives):

No payment or reimbursement will be provided to the patients for participation in this study.

Plan for obtaining informed consent

Either the primary investigator, co-investigators, or research assistants ("study personnel") will be on site to review scheduled outpatient colonoscopies on the morning of or afternoon of the scheduled procedure. Patients will be prescreened in UH Portal to determine if they meet inclusion and exclusion criteria. If identified as potential candidates, study personnel will approach patients after standard check-in procedures (changing into patient gown, review of medical history by nursing staff, intravenous line placement, etc.) have been completed. Privacy will be ensured during obtaining consent by offering to move to a private consultation room. Patients will be offered the opportunity to participate in the study with explanation of risks and benefits. They will be provided the opportunity to ask questions and will have ample time to determine whether they choose to participate. Please see the attached consent form to this of this protocol.

Provisions for subjects from vulnerable populations:

Employees of UHHS

Employees of UHHS will also be include as potential candidates for this study if they choose to participate. Extra caution will be taken to obtain consent in a private room where their decision to participate in the study or not to participate can remain discrete. In addition, we will follow the established protocol regarding deletion of identifying health information at completion of study enrollment.

Non-English Speaking or Illiterate Patients

There is minimal risk in participation of this study and the main purpose is to establish if there is a diagnostic benefit. If these patients are deemed candidates for inclusion into the study, the

appropriate translation and/or interpretation services will be employed to ensure complete and total understanding of the risks and benefits of participation in this study. For illiterate patients we will explain the study in clear and concise manner appropriate for the patient's level of understanding. If patients are unable to understand or provide informed consent despite these measures, they will not be included to participate in the study. It will be made clear to the patients that the care they receive will be in no way affected by participation in study and that no harm will come to them by choosing not to participate.

Data safety monitoring plan:

OVERSIGHT RESPONSIBILITIES
Oversight of the trial is provided by the Principal Investigator (PI), Dr. Parikh, and Drs. Rishi Sharma, Richard C Wong, Ashley Faulx, and Ygnve Falck-Ytter. ("co-investigators" throughout).

MONITORING PROCEDURES
Dr. Parikh assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB and FDA-approved research plan.

Study data are accessible online at all times for the PI and co-investigators to review. The PI and co-investigators review(s) study conduct including*:* accrual, drop-outs (if any, given that randomization will be done immediately prior to the procedure), and protocol deviations on a quarterly basis. The PI review(s) AEs individually real-time and in aggregate on a monthly basis. The PI and co-investigators review(s) serious adverse events (SAEs). The PI will visit each study site on a quarterly basis to ensure the protocol is being followed accurately at each site. The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB according to the applicable regulatory requirements. There are minimal AEs and SAEs expected however they are defined as below.

COLLECTION AND REPORTING OF SAEs AND AEs
For this study, the following AE definitions are used and are adapted from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE):

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of peppermint oil during colonoscopy that may or may not be considered related to peppermint oil itself.

AEs are graded according to the following scale:

Grade 1: Mild; asymptomatic or mild symptoms such as, but not limited to: abdominal cramping, bloating, mild nausea, diarrhea, constipation, or headache that do not require any intervention.

Grade 2: Moderate; symptoms such as, but not limited to: abdominal cramping, bloating, mild nausea, diarrhea, constipation, or headache that affect and limit age-appropriate instrumental activities of daily living (ADL), which refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc; symptoms as above where there a minimal, local or noninvasive intervention is indicated.

Grade 3: Severe or medically significant but not immediately life-threatening symptoms such as, but not limited to: an allergic reaction without evidence of anaphylaxis to peppermint oil which would require hospitalization and therapeutic intervention; hospitalization or prolongation of hospitalization for procedure related complications, or prolongation of hospitalization indicated;

disabling; limiting self-care ADLs, which refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4: Life-threating consequences such as a severe allergic reaction resulting in systemic anaphylaxis; severe acute end-organ damage including, but not limited to liver or renal failure; caustic injury to mucosa resulting in perforation requiring acute endoscopic or surgical intervention; and other scenarios were urgent intervention or transfer to ICU care is initiated.

Grade 5: Death related to AE.

Our study uses the following AE attribution scale:
Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
Related: The AE is clearly related to the study procedures.

Adverse events Grade 3 or higher will be reported to the IRB and FDA as soon as possible, but certainly within the required 15 days of the investigator being made aware of the event. In addition, all AEs are reported according to the UH IRB AE reporting guidelines.

Individual stopping criteria for study: Given the short duration of actual exposure to the interventional agent, 1.6% peppermint oil, we expect minimal

Overall stopping criteria for study:
1) If more than 5 patients develop the same CTCAE Grade 3;
2) If more than 3 patients develop the same CTCAE grade 4 or higher
3) If 1 or more patient develops CTCAE grade 5.

In the case that any of the above occur, the study will be stopped and the FDA and the respective IRBs will be notified of study stoppage. An investigation as to the causes for these events will ensue by the PI and co-investigators to determine if these events are related to the investigational agent, peppermint oil. The findings will be submitted to the FDA and the institutional IRBs.

Follow up after completion of procedure:
Patients will be followed up by telephone for assessments of adverse reactions at 24-48 hours after colonoscopy, one week after colonoscopy, and one month after colonoscopy. The patients will be contacted by either a physician who is involved as an investigator in the study or a research coordinator under the supervision of a physician who is involved as an investigator in the study. We will contact patients at intervals of 24-48 hours, one week, and one month after colonoscopy and use the attached telephone script to guide the conversation.

If on follow up assessment, there are adverse events thought to be Grade III or higher, we would request the patient to come back to be seen in clinic for further evaluation by the study investigators including laboratory testing and other diagnostic techniques as indicated by the patients clinical presentation.

The above plan has been discussed with and approved by the FDA IND committee.

Research data be stored by the PI after study closure for a period of:

3 years

Subject privacy

Provisions for protecting the privacy interests of participants or participants will include:

- All healthcare and research related discussions will be offered to occur in private and separate rooms to maintain privacy as per patient preference.
- Information collected and discussed will be limited to only the minimum amount of data necessary to accomplish the research purposes.
- After all data is collected, all patient identifiers will be removed to further protect privacy.

Data/Sample confidentiality plan

- Only study investigators will have access to identifiable patient health information.
- All hard-copy information will the stored in a storage locker, locked with combination lock, in the PI's office, which is locked by key in Wearn 220 (at University Hospitals)
- All patient health data collected from the study will be stored in RedCAP, a secure online database that meets the IRB data security and confidentiality requirements.
- All patient identifiers will be removed immediately after the completion of data collection.

Data/Sample security plan

- All Data will be collected electronically. No physical charts will be created. All information will stored in REDCap, a secure online database that meets the IRB data security and confidentiality requirements.
- Only study investigators will have access the REDCap database.
- The information will only be able to be accessed by study investigators listed in the personnel form in this IRB application.

Data Analysis Plan:

Descriptive statistics will be used for ADRs, total procedure time, withdrawal time, bowel prep scoring, and pain severity during procedure. The primary and secondary endpoints will be determined on an intention-to-treat basis. ADRs will be calculated based on results from pathology. Differences in ADR will be analyzed using chi-square test. No interim analyses will be performed. Resource use will be prospectively recorded in a disaggregated form.

This study is projected to enroll a total of 300 subjects (150:150) in group 1 and 2 respectively. Given a power of 80% and a confident level of 95% with a p-value of 0.05, to determine a 20% difference in ADR between both groups, a sample size of 274 is required.

Based on our internal review of our institutions experience with patients with poor preps and the very low Accounting for poor preps or withdrawal of consent, an increase in the sample size to 300 is projected. We estimate that approximately 1000 patients will be screened for participation in this study to accommodate for patients that are not interested or not candidates for the study.