THE EFFECT OF ADDING HIGH DOSE SIMETHICONE TO A STANDARD POLYETHYLENE GLYCOL PREPARATION ON ADENOMA DETECTION RATE DURING SCREENING COLONOSCOPY: A RANDOMIZED CONTROLLED PILOT TRIAL

ABSTRACT

Screening colonoscopy is a procedure that can effectively prevent colorectal cancer. Adequate mucosal visualization is a critical aspect of this procedure and yet, several factors can interfere with it and consequently result in missed lesions. One of the most commonly encountered factors affecting mucosal visualization is a poor preparation and/or the presence of multiple bubbles at the time of colonoscopy. When a large amount of bubbles is found, simethicone (SIM) is commonly injected through the colonoscopy in order to eliminate them and get a better view of the mucosa. However, this practice has been recently associated with outbreaks of multi-drug resistant bacterial infections, in several endoscopy centers. A few studies have used SIM in conjunction with colon preparation agents (CPA) such as polyethylene glycol (PEG), magnesium citrate, and sodium phosphate, in an attempt to improve the overall quality of the preparation. Unfortunately, these studies have reported conflicting results due to a wide heterogeneity in their methodology and each study has used different CPAs and SIM doses. Furthermore, with the exception of one recently published study from China, no study in western literature has reported an increase in adenoma detection rate (ADR) when SIM is added to a CPA. Given this gap in knowledge, we are planning to conduct a pilot study to determine whether adding a high dose of SIM to a CPA results in a statistically significant difference in ADR.

SPECIFIC AIMS

The study's primary aim is to establish if the ADR improves with the addition of high dose SIM suspension to a polyethylene glycol (PEG) preparation. Secondary aims are to determine if this intervention results in shorter withdrawal times, better colon preparation, less intra procedure use of SIM and a higher polyp detection rate (PDR).

BACKGROUND/SIGNIFICANCE

An adequate bowel preparation is paramount for a screening colonoscopy. Mucosal visualization can be dramatically affected by residual stool, bubbles, bile, intraluminal fluid or debris (1, 2). Any of these features can ultimately lead to missed lesions, prolonged endoscopy duration, and decreased patient tolerance. PEG is one of the most commonly used CPAs. A few studies have reported that the addition of low to medium doses of SIM to lower volume PEG regimens (2L) or other CPAs such as sodium phosphate results in overall better colon preparations based on a standardized bubble scale (BS) and Boston preparation scales (BPS) (3-9). Some of these studies have also reported a trend towards a higher number of polyps detected in the patients who added SIM to their CPA. This finding did not reach statistical significance likely due to the fact that they were neither powered enough nor primarily designed to do so.

It is important however, to understand that SIM is not a CPA. It is and anti- foam medication and its purpose is to decrease the amount of bubbles interfering with visualization, provided that there is no stool present. In clinical practice, it is very common to use it as a flush through the endoscope at the time of the procedure for that purpose. Nevertheless, such use of SIM has been recently associated with the formation of biofilm inside the endoscope's operative channels that is not eliminated by standard disinfecting and reprocessing techniques (10). This biofilm leads to persistent moisture that has been noted as a contributing factor to outbreaks of multi-drug resistant microorganisms in a few high level endoscopy centers (11).

In summary, previous studies have shown a trend towards a better overall preparation, and a higher polyp detection rate when a low to medium dose of SIM is added to a CPA. Therefore, the present pilot study is designed to determine if adding high dose SIM to a regular 4L PEG has the potential to positively impact the ADR, a benchmark quality indicator of screening colonoscopy. Adding a high dose SIM to a CPA could not only result in a higher ADR, but also in a decrease use of SIM through the endoscope at the time of the procedure, reducing the risk of possible life threatening infections for future patients.

The intervention in this study although simple and inexpensive has the potential of making a significant impact in the health of our already underserved population. Our health sciences center is the only academic medical facility performing clinical and basic science research in southwest Texas and we serve a large number of patients, most of which are Hispanic Americans with only limited access to healthcare.

RESEARCH PLAN

Study Design:

This is a single-center, prospective, randomized controlled, observer-blinded study of patients undergoing screening colonoscopy at a tertiary care medical facility.

Primary endpoint

To establish if the ADR improves with the addition of high dose SIM suspension to a polyethylene glycol (PEG) preparation

Secondary endpoints

1. Determine if adding a high dose of SIM to PEG reduces the withdrawal times during the screening colonoscopy.
2. Determine if adding a high dose of SI to PEG results in an overall better colon preparation.
3. Determine if adding a high dose of SIM to PEG results in less intra-procedural use of SIM.
4. Determine if adding a high dose of SIM to PEG results in a higher polyp detection rate

Inclusion criteria:

1. Patients between the ages of 30-75 scheduled for screening colonoscopy.
2. Male and female patients

3. Ambulatory patients
4. Signed informed consent form
5. Colonoscopy performed by an attending gastroenterologist
6. The use of both Moderate Sedation and Monitored Anesthesia Care (MAC) sedation

Exclusion criteria:

1. Previous colonic surgery
2. Patient with mental/physical condition that impairs oral ingestion of preparation
3. Allergy or hypersensitivity to simethicone
4. Patients with limited mobility (bedridden patients)
5. Patients with gastrointestinal obstruction
6. Patients with GI motility disorders(e.g. achalasia, gastroparesis, chronic constipation)
7. Colonoscopy performed by GI fellows

Patient Enrollment:

Enrollment will be done prospectively until the desired number of patients is reached. This study is planned as a parallel group randomized trial. One group of patients will be randomized to SIM plus PEG while the other group will be randomized to PEG only. The dose of SIM that will be used in this study is 480 mg (2-times higher than the dose used in previous studies). The rationale for using a high dose is to maximize our outcome yield. Our proposed sample size is 300 patients. In our unit, we perform approximately 60 screening colonoscopies per week. We anticipate that approximately 10% of these patients will be eligible to participate in the study. Therefore, we expect to enroll the desired number of patients in approximately 24 months.

Data Collection:

For each patient, the following data will be collected:

1. Age (years)
2. Gender (male/female)
3. Ethnicity (Hispanics/non-Hispanics)
4. Past medical and surgical history (yes/no)
5. Bowel preparation quality (poor, fair, good, very good, excellent)
6. Boston preparation scale score
7. Bubble scale score
8. Cecal intubation time (minutes and seconds)
9. Withdrawal time (minutes and seconds)
10. Effective procedure time (minutes and seconds)
11. Number and size of polyps detected
12. Number of adenomas detected

13. Intra-procedure use of SIM

Sample size calculation

The dose of simethicone that will be used in this study is 480 mg (2-times higher than the dose used in previous studies). The rationale for using a high dose is to maximize our outcome yield. Our sample size calculation was based on articles by Yoo et al [8], Jansen et al [9] and Bai et al[10] using the following formula considering ADR as the primary outcome:

$$n = 2\frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \overline{pq}}{\left(p_1 - p_2\right)^2}$$

Where p1 was the % of outcome in the intervention group and p2 the % of outcome in the control group. Bai et al[10] reported ADR of 21.0% in the PEG+SIM group and 14.3% in the PEG group. With these results, a sample size of 509 per group would be suitable for the parent study. For the pilot study, 10% of the calculated sample size for the parent study would be an acceptable estimation [13]. Considering the heterogeneity of the study by Bai et al, we decided to include 20% of the total calculated sample size in this pilot study. Therefore, 102 patients per group would be an appropriate sample size to compare ADR in this pilot study.

Other outcomes to explore in the current study include preparation quality and PDR. Yoo et al [8] reported that 99% of patients receiving PEG+SIM had BPS scores of 6-9 compared to only 84% in the patients who received PEG. Considering BPS scores as the outcome (p1=99% and q1=84%), with α=0.05 and β=0.2, a total of 110 patients will be needed, 55 in each arm. On the other hand, Jansen et al [9] reported that PDR in patients who received PEG+SIM was 26.7% compared to 13.7% in those who received PEG. With these results and following the same formula, a sample size of 150 patients per group will be needed to evaluate both bowel preparation and PDR. Therefore, in order to have a sufficient study power and examine all parameters (ADR, PDR and bowel preparation quality), we decided to include 150 patients per group for a total of 300 patients.

Statistical analysis

1. Continuous data (e.g. effective procedure time, withdrawal time) will be described using mean and standard deviation (SD) or Median (Q1, Q3) based on D'Agostino-Pearson normality test in each group and will be compared with either independent t-test or nonparametric Mann-Whitney. Interval data (e.g. BPS, BS) will be presented as Median (Q1, Q3) in each group and compared with nonparametric Mann-Whitney. Categorical data (e.g. ADR) will be described using frequency and proportion (%) in each group and will be compared using Chi-square or Fisher's exact test where appropriate. Further, number needed to treat (NNT) using SIM+PEG will be determined. Cohen's kappa coefficient will be used to measure inter-rater agreement between two endoscopists who will score BS and BPS. In the eventual presence of baseline differences in cofactors, a relative risk regression developed by our biostatistician[14] will be used

to determine adjusted effect of SIM+PEG compared to PEG alone on PDR and ADR. Other findings at colonoscopy

All the statistical analyses will be performed using STATA 14 and p-values less than 5% will be considered significant results. All the statistical analyses will be performed by our Biostatistics and Epidemiology Consulting Lab (BECL) under the supervision of Dr. Dwivedi.

METHODS

Patients will be included in the study in a prospective manner at University Medical Center of El Paso endoscopy unit. At the time of the pre-op appointment, the assessment nurse will provide all patients with routine instructions for colonoscopy including diet, hydration and fasting. At the same appointment, the research coordinator, and/or an investigator will consent the patients and the research coordinator will randomize them using a random number list generated by a simple block randomization scheme by our study statistician, to one of two possible preparations: PEG+ SIM or PEG alone. The randomization will be via sealed envelopes that will contain cards with the type of preparation to be used. These coded envelopes will be randomly chosen by the patient. Following randomization each patient will be assigned a code corresponding to one of the two preparation regimens. This code will be noted and placed in a master spreadsheet that only the study coordinator and/or assigned research personnel will handle. The simethicone and instructions will be provided to the patients by the research coordinator. Patients randomized to PEG+SIM will drink 2L of PEG at 5 PM the evening before colonoscopy, and 2L 4hrs prior to the colonoscopy. Patients in this group will be instructed to fill a standard 0.6 ml dropper with SIM suspension (40 mg/0.6 ml) a total of 12 times and add it to the gallon of PEG solution. Patients assigned to PEG will drink the preparation in the exact same manner but without SIM.

Prior to the procedure, a safety assessment of each patient will be completed which will include vital signs and a general examination. Patients will also complete a questionnaire evaluating compliance and side effects from the preparation. This questionnaire will be administered and collected by an assigned research team member. The patients will be instructed not to disclose any information regarding the preparation regimen to the endoscopist or any of the procedure nurses.

Colonoscopies will be performed by 4 experienced endoscopists who will be blind to the type of preparation the patient received. All procedures will be performed using Olympus 190 colonoscopes. During colonoscopy, standard parameters such as cecal intubation time, withdrawal time and number of polyps detected will be recorded. For the purpose of this study, withdrawal time will be measured as follows: the timer will be started upon initiation of endoscope withdrawal once the cecum has been reached, and it will be paused every time the endoscopist needs to perform any maneuver or intervention such as polypectomy, biopsy, clip placement, hemostasis, suction for >5 seconds etc. Once the endoscopist is done performing any of these, the timer will be re-started. Endoscopists will be free to ask for SIM during the procedure if he/she deems it necessary and the amount will be recorded by the research coordinator. In addition, endoscopists will be asked to score the preparation according to

the standardized BS (0-3; 3 being the worst) and the BPS (3-0; 3 being the best) . A total BPS score of >6 and a BS of <2 will be considered adequate preparations.

The BS that will be used in this study is the one previously used by Sudduth et al (7). This score grades different sections of the colon as follows: 0 = no or minimal, scattered bubbles believed not to be interfering with the examination; 1 = bubbles covering at least half the luminal diameter; 2 = bubbles covering the circumference of the lumen; 3 = bubbles filling the entire lumen. The overall BS and BPS scores will be determined by adding the scores of each segment of the colon (rectosigmoid, transverse and ascending). For example, in a patient whose individual segment BS scores are as follows: 0,2,1; the final score is 3. All endoscopists will be trained in the use of both scales prior to their participation in the study. The bubble scale and the BPS scores will be independently determined by the endoscopist performing the procedure and by a second endoscopist who will review the still previously selected and labeled by the performing endoscopist and will assign his own score based on these images. Each endoscopist will be blind to the score provided by the other one and inter-observer agreement will be calculated.

The ADR will be calculated once the pathology results of the polyps removed become available.

INNOVATIONS

To the best of our knowledge, this is the first study designed specifically to evaluate the effect of high dose of SIM in conjunction with 4 L PEG preparation on ADR in a western population. Our pilot design will produce rapidly available data that will be then used to design a full sized trial that will definitively confirm or refute our hypothesis, which is that adding SIM to PEG improves ADR. Our study is innovative in its methodology in the following aspects: 1. It is the first one to use a 4 L PEG preparation in both arms (previous studies have used 2 L PEG or other CPAs); 2. It is the first one performed in a standardized average risk western population undergoing screening colonoscopy (previous studies have included both screening and diagnostic colonoscopies); 3. It is a randomized controlled trial and its proposed methodology is a cost-effective approach compared to other alternatives; and 4. Inter-observer agreement of both BPS and BS will be calculated, reducing the potential for bias.

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