Study Protocol for
Comparison air versus carbon dioxide insufflation in single balloon anterograde enteroscopy

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Significance/Background:

Endoscopy is a valuable tool utilized by gastroenterologist to inspect the length of the gastrointestinal tract. The gastrointestinal tract is a hollow viscous and is contracted in its normal state. In order to expand a contracted portion of the gastrointestinal tract insufflation is required. Two approaches utilized in insufflation are air and carbon dioxide (CO2). The vast majority of endoscopy utilize air insufflation given it ease and lower cost. It's increase retention in the lumen provides good expansion, however, with prolonged endoscopic procedures side effects from air insufflation can occur symptoms such as abdominal pain, nausea, and bloating/abdominal distention are a result of the retention of air in the lumen.

Carbon dioxide is the alternative to air insufflation. It is commonly used gas utilized in many fields of medicine most commonly in laparoscopic and endoscopic procedures. CO2 in the GI tract is absorbed about 160 times greater than nitrogen (the major component of insufflated air). Once the CO2 is absorbed through the mucosa of the GI tract it crosses into the bloodstream and is exhaled through the lungs.[3,5] This rapid absorption coupled with the potential vasodilatory effect of CO2 in mucosa seen in animal studies are believed to be the reason behind reduced post procedural distension and pain.[4,5]

There are 9 randomized controlled studies which have evaluated CO2 insufflation gas; 6 of them studying colonoscopy and the others involve either sigmoidoscopy, ERCP, and double-balloon endoscopy. All of which find CO2 to be superior with patients experiencing less pain and bowel distension.[3] CO2 insufflation is considered by many endoscopists to be superior to air insufflation and its use is actually advocated by American Society for Gastrointestinal Endoscopy (ASGE) as the insufflation gas of choice for procedures that carry a high risk of perforation.[3,6,7,8] Although CO2 insufflation has its reservations primarily in those patients with predisposed pulmonary conditions due to their reduced ability to expel carbon dioxide, many early studies had even excluded patients with known pulmonology diseases. Crossover trial data and 2 additional studies that evaluated the safety in CO2 insufflation in patients with diminished pulmonary function showed no significant difference in the rise of ETCO2, during or after the procedure and adverse events were similar between both patient arms of both studies. THIS NEEDS TO BE BEEFED UP AND WITH CITATIONS

CO2 insufflation has been demonstrated safe, effective, and capable of reducing patient's post procedural symptoms in multiple studies involving colonoscopy, flexible sigmoidoscopy, ERCP, balloon

assisted enteroscopy and endoscopic submucosal dissection.[1,2,3,9,10,11] Despite the vast amount of literature on air versus carbon dioxide insufflation there is limited data for single balloon anterograde enteroscopy. Our hypothesis is that anterograde single balloon enteroscopy that utilizes carbon dioxide insufflation will have fewer symptoms of abdominal pain, nausea, and bloating as compared to air insufflation.

Objective(s): Identify if the use of carbon dioxide insufflation can reduce the amount of post-operative pain, nausea, and bloating with single balloon endoscopy.

Primary Outcome Variable(s):

1. Does the use of carbon dioxide for insufflation reduce the amount of postoperative pain compared to air insufflation?

Secondary Outcome Variable(s):

1. Average time of procedure air vs carbon dioxide insufflation.
2. Type and amount of anesthetic used air vs carbon dioxide insufflation

Setting/Resources for the Study:

Procedures are to occur at St. Joseph's operating room. The electronic medical record will be accessed by Dr. Thomas Geisler and Dr. ZK to obtain the necessary information. The investigators have all participated in research at St. Joseph's previously and have successfully completed the CITI program. The balloon endoscopies will be performed by Dr. MD M.D. with assistance from one of 3 GI fellows, RC D.O., TG D.O., or JC. The timeframe set for this study is a 1-1.5year study with a goal of 50-80 patients. To obtain a significant power it is calculated to obtain a sample population of approximately 350 patients. Given the infrequency of this procedure this number is unlikely to be obtained, however the information gleaned from this study could still contribute to further studies and analyses.

Study Design: Prospective Observational Study

Study Subjects:

All patients >18 years of age who presented to North Eastern Ohio Gastroenterology and Associates and meet the indications for anterograde or retrograde balloon endoscopy. Indications include small intestinal bleeding, evaluation of small bowel mass, or evaluation and treatment of small bowel strictures. Patients excluded from the study are those who wish not to participate, pregnant patients, mentally disabled individuals, prisoners, patients who have long-term analgesic use (greater than 3 months) in the past 6 months from procedure date, or those patients deemed too high risk to undergo balloon endoscopy. High risk patients will be defined as have 3 or more of the following risk factors: chronic obstructive pulmonary disease, renal failure, morbid obesity (BMI > 40), immunosuppression, acquired/concurrent infection, diabetes, and chronic steroid use. Pre-operative risk will also be assessed by Dr. MD M.D. and GI fellow. ASA classifications will be evaluated on every patient by St. Joseph's staff anesthesiologist. Given that the patient is receiving general anesthesia, it is hospital policy that they are evaluated at the hospital by anesthesia team prior to the procedure for assessment of risk. Should a patient elect not to participate in the study they will receive the standard of care.

Subject Recruitment/Screening/Consent:

Patients will be recruited/consented/randomized by the GI fellow and Dr. MD M.D. during the patient's routine office visit to discuss their pending procedure. This will take place in a private consultation room to ensure privacy and should take approximately 10-15 minutes. In order to minimize coercion, it will be

made very clear to patients that their participation is voluntary, and that participation will in no way affect their future care. Randomization will be performed using a sealed envelope system. All patients are to receive a copy of the informed consent.

Study Procedures:

The single balloon enteroscopy is performed with Olympus (SIF-Q180) and operated by a single experienced endoscopist, Dr. MD M.D., with over 1,000 single balloon endoscopies have been performed. Additional assistance provided via 3 gastroenterology fellows (RC D.O., TG D.O., and JC D.O.). All anterograde enteroscopy procedures are to be performed in the surgical suite with general anesthesia. Patient CO2 levels will be noninvasively monitored by anesthesia with End-Tidal Carbon Dioxide (ETCO2). Anesthesia will be administered at the discretion of the consulting anesthesiologist via fentanyl, versed, and propofol. Insufflation utilized during procedure determined via randomization to air or carbon dioxide prior to procedure. The rate of air or carbon dioxide (level) is left to discretion of acting endoscopists for proper insufflation of bowel to achieve adequate luminal views. CO2 insufflator to be used is a Stratus CO2 insufflator made by Medivators.

After completion of procedure determination of patient pain level will be assessed at 15 minutes, 30 minutes, and 1-hour and 24-hour intervals using a patient survey. Pain is assessed based on the horizontal assessment scale (HAS). This scale based on a horizontal line measuring 100mm in length. Patient will be asked at the afore mentioned time intervals to mark with pen their level of pain on the HAS. The mark will then be measured in millimeters to determine score of pain. Score will be in a range from 0 to 100mm. Zero being no pain at all and 100mm the maximum pain level. The HAS is then documented with type of insufflation utilized and time interval. Patient will also be asked about nausea, abdominal fullness, and bloating after procedure to be ranked on a 0 to 10 scale, with zero being nothing to 10 as severe. This will also be ascertained at 15 minutes, 30 minutes, 1 hours and 24 hours. The 24 hours assessment for pain as well as dyspepsia symptoms is achieved through patients receiving HAS scale along with a questionnaire asking to rank dyspeptic symptoms. The HAS scale and dyspeptic questionnaire will be marked with patient identification number. A self-address envelope with postage will be given to patient with instruction return once completed within 24 hours of original procedure. Instruction sheets along with how to take dyspeptic survey will also be given.

Data collected from the chart will include patient demographics, operative technique, complications.

Standard of care follow-up will occur at the outpatient office with Dr. MD M.D. and GI fellow.

Early Withdrawal of Subjects:

A patient may withdraw at any time from the study and data that had already been collected on these patients will still be used.

Sample Size Determination:

The primary outcome variable is improved patient pain, bloating, abdominal fullness, and nausea. Previous studies show varied sample sizes, from 40 total patients to 300. Our goal is 25-40 persons in each procedure group, for a total of 50-80 patients.

Statistical Methods:

Data will be entered into Microsoft Excel 2017 and SPSS version 22 statistical programs. Analysis will include descriptive statistics, t-test, standard error, Pearson and fisher exact test. Statistical significance will be established with α of 0.05 for all comparisons.

Potential Benefits:
While nothing can be guaranteed, the hypothesis is that patients in the CO2 insufflation group may experience less pain, bloating, and nausea. The patients may not benefit from their participation in this study.

Adverse Events:
Risks consist of those entailed with general anesthesia and single balloon endoscopy.
The risk of CO2 insufflation consists of respiratory depression and CO2 embolism.[16]

Recording of Adverse Events:
At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately (e.g., signs, symptoms, abnormal diagnostic procedures). The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Reporting of Serious Adverse Events
Reports of all serious adverse events (including follow-up information) will be submitted to the St. Elizabeth's Mercy Health IRB within five business days.

Data Management and Confidentiality
Patient data will be entered into electronic spreadsheets. The spreadsheet will be stored as separate file, protected by unique passwords. Only the investigators will have access to the files and their passwords. Paper records will be stored in hard copy in a locked filing cabinet in the investigator's office or at the hospital's endoscopy suit. Should any new significant findings be made during the study, the patient will be made privy to these findings in a timely manner.

Provisions to Protect the Privacy Interests of Subjects
Patient consent and all other research related activities will take place in a private exam room. Patient will also be receiving a copy of their informed consent.

Funding Source:
No funding is being sought for this study or being received.