ID: 30114 Cystic Fibrosis and Gut Dysmotility: The Effect of Polyethylene Glycol (PEG) on Intestinal Transit NCT04210427

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Background:

Cystic Fibrosis (CF) is an autosomal recessive disorder involving mutation of the cystic transmembrane conductance regulator (CFTR) protein. The consequence of this genetic mutation leads to dysregulated epithelial fluid transportation. Abnormalities of the CFTR protein have multisystem motility complications - it affects primarily the lungs, pancreas, vas deferens, and the gastrointestinal (GI) tract. Cystic Fibrosis causes multiple issues in the GI tract. The CFTR protein is expressed throughout the GI tract at the apical enterocyte membrane. Per recent studies, it has the highest concentration in the duodenum and decreases as the small bowel terminates into the large intestine (1). Patients often experience symptoms secondary to dysmotility from abnormal salt and water regulation into the gastrointestinal lumen. Cystic Fibrosis patients are at risk for small intestinal bacterial overgrowth (SIBO), intestinal dysbiosis, inflammation, distal intestinal obstruction syndrome (DIOS), constipation, and postprandial delayed gastric emptying.

Multiple studies have been done to evaluate gastrointestinal motility in CF patients. Bentur et al studied gastric muscle rhythms in CF patients via pre- and post-prandial electrogastrography (EGG) and found postprandial bradygastria (2). Patients had symptom improvement with initiation of cisapride however this drug is not FDA approved in different continents. Hedsund et al studied GI transit times via the magnet-based motility tracking system and found increased transit in the upper small intestine compared to control populations (3). Overall, CF patients were found to have delayed small intestine transit time with the magnetic pill reaching the cecum in only 2 of 10 CF patients in a 7-hour period compared to 14 of 16 control patients. Hydrogen Breath tests have diagnosed SIBO in CF patients however overall delay in intestinal transit affect interpretation of results. Empiric treatment with antibiotics or laxatives is recommended with some improvement in patient symptoms. Mouse studies have shown that use of Miralax (brand name) or polyethylene glycol (PEG) laxative decreased bacterial overgrowth in 90% of Cystic Fibrosis mice1. Further studies showed that daily PEG use decreases positive breath tests in a small study of CF patients. While there have been multiple studies showing symptomatic improvement of SIBO and DIOS with PEG and/or other laxative agents, none have measured whether these medications improve intestinal transit time.

Objective: The main goal of this research project is to evaluate total intraluminal transit time in CF patients and the effects of PEG on transit time and patient symptoms. Primary outcomes include gastrointestinal transit time and symptom improvement.

Design and Methods:

This is a prospective cohort study. This is also an investigator-initiated study. Once enrolled, patients will spend 4 weeks in the study. All participants will receive the intervention. There will be no randomization in this study. Information pulled from the patient's medical record includes the patient's name, medical record number, date of birth, cystic fibrosis genotype, medication list, and medical history.

Study Protocol

1. Initial recruiting visit: Informed consent to participate in the research study will be obtained. The patient will need to have a 2-week washout period where all non-essential medications that alter gut motility are temporarily stopped. The medications withheld will be at the discretion of the physician. This list will be provided to the patient. The patients on pancreatic enzyme replacement must remain on this so as to not affect study outcomes.

   2. Second visit: The patient will complete Rome IV Diagnostic Questionnaire for Adult FGIDs (R4DQ); This Questionnaire is considered a research procedure. Once procedural informed consent is obtained, the patient will be fitted for the recorder and ingest the SmartPill. The patient will return the receiver up to seven days after the capsule was ingested. The SmartPill is considered a research procedure. If the SmartPill is not excreted after day 7, the patient will obtain an outpatient abdominal X-ray to determine if the SmartPill device is retained in the intestines. A pregnancy test will be performed prior to any potential radiation exposure for female patients of child-bearing ages, 13-50 years old. The X Ray, if completed, is considered a research procedure.
   **If there is concern the SmartPill may be retained in the intestine, the patient may be asked to take a Patency agile capsule. This will require the patient to obtain a abdominal X Ray 24 hours after ingestion as an outpatient to localize the capsule's location. This is considered standard of care.

   3. Study period (two weeks): After 7 days, the patient will begin intervention with polyethylene glycol (PEG) 17 g therapy for total of 2 weeks. If persistent symptoms (no bowel movements in > 24 hours, abdominal pain, straining, bloating), then the patient can increase to 17 g twice daily. The patient will call the office after 1 week to determine if step up to twice daily therapy is warranted.

   The patients will receive a log to record time of PEG ingestion, if PEG was taken with meals, a log of other medications taken during the intervention timeline and recording symptoms of constipation. Patients will be advised to avoid non-essential

drugs that can alter gut motility (see attached list found on the patient log) during the treatment period. The study drug is considered standard of care procedure.

4. Third visit: Two weeks following initiation of therapy, the patient will repeat the Rome IV Diagnostic Questionnaire for Adult FGIDs (R4DQ) and ingest the second SmartPill to assess for change in gut motility. Procedural informed consent will be obtained prior the questionnaire and ingestion of the SmartPill. This Questionnaire and SmartPill device is considered a research procedure. The patient will return the receiver up to seven days after the capsule was ingested.The SmartPill is considered a research procedure. If the SmartPill is not excreted after day 7, the patient will obtain an outpatient abdominal XRay to determine if the SmartPill device is retained in the intestines. A pregnancy test will be performed prior to any potential radiation exposure for female patients of child-bearing ages, 13-50 years old.The X Ray, if completed, is considered a research procedure. **If there is concern the SmartPill may be retained in the intestine, the patient may be asked to take a Patency agile capsule. This will require the patient to obtain a abdominal X Ray 24 hours after ingestion as an outpatient to localize the capsule's location. This is considered standard of care.

5. Fourth visit: The patient will return the recorder equipment for analysis and will complete a post study questionnaire and undergo review of their therapy log detailing how the medication was taken. This Questionnaire is considered a research procedure.

The subject participation in the study ends at this point.

Statistical Plan:

The data analyzed includes SmartPill endoscopic studies and Rome IV Diagnostic Questionnaire for Adult FGIDs (R4DQ). Statistical analysis will compare the relationship of GI transit time pre and post treatment.

Statistical Analysis

Final statistical analysis will be completed with a Department of Health Sciences statistician. Results are considered statistically significant using a p value of <0.05 alpha level.

Due to less-than-optimal numbers of participants, this study was closed after enrolling three patients. Therefore, the above statistical methods could not be applied. No data analysis was performed due to insufficient data.