A Prospective Randomized Control Trial of The Effectiveness of Entereg as a Rescue Treatment of Postoperative Ileus Following Colorectal Surgery

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Objectives

Primary:

- To determine the efficacy and safety of Entereg for the treatment of post operative ileus following colon or rectal resection.

Secondary

- To determine the effect of Entereg as rescue therapy postoperative ileus on hospital length of stay, return of bowel function, and 30-day outcomes.

Clinical hypotheses

Entereg can be given to patients after the development of post operative ileus to reduce the duration of ileus and shorten hospital stay.

Postoperative ileus (POI) is one of the most common complications following abdominal surgery, and a frequent cause of prolonged hospitalization [1]. The exact mechanisms of POI, defined as the prolonged transient impairment of bowel motility, are not well defined and are likely multifactorial [2,3]. The most commonly cited factors leading to the development of POI are disorganized electrical activity, sympathetic inhibitory neural reflexes, release of proinflammatory mediators, excessive intravascular volume, and the use of opioid analgesia [4,5].

A variety of perioperative strategies have been developed to help prevent the development of and/or reduce the duration of POI. These strategies have been incorporated into most Enhanced Recovery After Surgery (ERAS) pathways, and include avoidance of mechanical bowel preparation, use of laparoscopy when feasible, IV fluid restriction, no routine nasogastric tube placement, early feeding and ambulation after surgery, and limiting opioid use [6,7]. Several pharmacologic agents have been studied as means to prevent POI. The most successful of these is Entereg, a peripheral opioid antagonist, currently approved for use in open bowel resection. Given preoperatively and continued postoperatively until return of bowel function, Entereg has been shown to reduce the incidence of POI, shorten hospital stay, and is associated with lower postoperative morbidity and readmissions compared to placebo [8-10].

Currently there are no effective treatments for POI ileus after it develops.
Numerous prokinetic agents, including erythromycin, cholecystokinin, lidocaine, and neostigmine, have been used in randomized control trials, yet none have been shown to reduce the duration of POI [11]. The use of laxatives has also been investigated as a potential treatment for POI. In one randomized trial, the use of bisacodyl after surgery led to significantly accelerated gastrointestinal recovery compared to placebo, however, the trial included all patients undergoing surgery and not just those who developed POI, and so the benefit of laxatives as a treatment modality remains unclear [12].

Despite significant advances in prevention, POI continues to be a clinical issue. In our own practice, despite a robust ERAS pathway, POI occurs in approximately 10% of patients undergoing bowel resection, increasing hospital stay by an average of five days. For these patients, current treatment includes bowel rest, reduction of oral diet, and possible nasogastric tube placement while waiting for the

POI to resolve directed pharmacologic treatment could potential expedite the return of bowel function, reducing length of stay and increasing patient comfort.

The benefits of developing a treatment for post operative ileus are substantial. As opposed to prophylactic treatment, all patients without contraindications could be treated. This would reduce the use of unnecessary treatments in patients who do not develop POI. The decrease in patient discomfort, prolonged hospital stay would be significant. In addition, there is a financial cost to POI. The Health Care Financing Administration estimates that $1.14 billion dollars are spent annual on postoperative ileus.

Despite extensive evidence for use in the prevention of POI, no formal studies have been performed to investigate the efficacy of Entereg as a rescue treatment of ileus after it develops. However, based on our use of Entereg inpatients with postoperative ileus, we have seen a rapid return of bowel function, decrease in placement of nasogastric tube and earlier discharge from hospital. A randomized control trial would provide concrete evidence of this anecdotal success and potentially lead to the first clinically effective pharmacologic rescue therapy of POI.

Study Overview
This will be a prospective randomized control trial with a total of 142 patients. Patients who undergo laparoscopic or open colorectal resection, small bowel resection, or ileostomy reversal with small bowel resection that subsequently develop postoperative ileus will be eligible for enrollment. If they meet inclusion/exclusion criteria, they will be randomized at the time of diagnosis of postoperative ileus to receive Entereg as rescue therapy or to receive conservative standard care.

Patients randomized to the Entereg group will be given 12mg of Entereg two times daily from the time of randomization until the return of bowel function or 5 days. Both groups will be treated with conservative standard care, including bowel rest, reduction in oral diet, and placement of nasogastric tube as clinically indicated.

All patients will follow a standard ERAS pathway after surgery, with early feeding and ambulation, along with opioid minimizing measures as is our standard postoperative protocol.

Primary outcome will be hospital length of stay.
Secondary outcomes will include time to return of bowel function, 30-day morbidity/mortality, complications, reoperation and readmission.

Total number of patients: 142
Patients in each study group: 71

Inclusion criteria

1. Subjects who have benign or malignant colonic or rectal disease that have undergone laparoscopic or open colorectal resection, small bowel resection or ileostomy reversal with small bowel resection and subsequently developed postoperative ileus, defined as:
    a. Return to NPO status after initial diet attempts, or
    b. Placement of nasogastric tube
2. Subjects who are 18 years of age and older
3. Subjects of either gender
4. Subjects who are willing and able to adhere to protocol requirements, agree to participate in the study program and provide written and informed consent.

Exclusion criteria

1. Subjects who received Entereg preoperatively.
2. Subjects that have taken therapeutic doses of opioids for more than 7 days immediately prior to surgery.
3. Subjects with severe hepatic impairment.
4. Subjects with end-stage renal disease.
5. Subjects who are pregnant.

6. Subjects who were diagnosed with a complete small bowel obstruction preoperatively.
7. Subjects with a medical condition that may interfere with the use of the study medication Entereg.
8. Subjects who have a condition or general disability or infirmity that in the opinion of the investigator precludes further participation in the study
9. Subjects with an ostomy

Study Calendar	Screening	Remaining Hospitalization	30 Day Follow-up
Enrollment Criteria	x	x	
Study Group Assignment	x		
Informed Consent	x		
History and Physical	x		
Collection of demographic data	x	x	
Monitoring for return of bowel function		x	
Administration of Entereg 12mg PO BID or conservative management		x (until return of bowel function)	
Enhanced Recovery Program (ERP)		x	
Complications/ Adverse events		x	x

Recruitment

Patients will be recruited from the University Hospitals Case Medical Center Division of Colorectal Surgery in Cleveland, OH. The patient population in this study will be candidates of either sex, over 18, who have benign or malignant colonic or rectal disease in which resection was performed via an open or laparoscopic approach, small bowel resection or ileostomy reversal with small bowel resection and primary anastomosis and subsequently developed postoperative ileus. The diagnosis of postoperative ileus will be made by meeting one or more of the following criteria: 1) return to NPO status after initial attempts at oral diet, 2) placement of nasogastric tube after surgery. Patients will be recruited until at least 142 participants are enrolled unless the study is halted prematurely by the safety monitoring board. The investigators will discuss the study with potential subjects prior to surgery date. The potential subjects will be given an information sheet to provide information about the study prior to surgery as part of their pre-op packet. This will give patients an opportunity to review information on the study in the event they are diagnosed with an ileus and approached to participate.

Enrollment and Consent
Enrollment will take at the time of diagnosis of postoperative ileus. The patients will be asked to participate in the study after evaluation by either the PI or the co-investigators. The investigator and study coordinator will discuss the study with the patient and informed consent will be obtained. Patients will be assigned a unique study identification number.

Randomization
Randomization will take place following enrollment and consent. A numbered, sealed envelope, corresponding to the patients' assigned study number, will be opened by *the study coordinator* indicating to which study group the patient is randomized. The study coordinator will notify the pharmacy which study group the patient has been randomized to. Randomization will be stratified to open or laparoscopic surgery, location of surgery (right/left), stoma reversal and presence or absence of stoma. *This will be kept in a locked key to be revealed at the end of the study.*

Enhanced Recovery After Surgery Pathway
All patients will be managed via standardized accelerated postoperative recovery guidelines, which are currently in use by the division of colorectal surgery at UHCMC. This includes patient-controlled analgesia pump, oral analgesia and diet on the first postoperative day, early postoperative ambulation, and defined discharge criteria.

Study Methods
At the time of diagnosis of postoperative ileus and after enrollment and randomization, all patients will be returned to NPO status. Nasogastric tubes (NGT) may be placed for gastric decompression at the discretion of the surgical team if clinically indicated. In the event that an NGT is placed, medications will be given orally or via the NGT, which will be clamped for 30 minutes after administration. Patients will continue on standard ERAS pathways with the exception of reduction of diet. Antiemetics will be given as clinically indicated; however, no prokinetic or promotility agents will be given as scheduled dosages.

Patients randomized to the study group will be given 12mg of Entereg orally twice a day, from the time of diagnosis of postoperative ileus to the time of return of bowel function and tolerating solid food without vomiting or experiencing significant nausea within 4 h following the meal, or without having to revert to enteral fluids only or for 5 days.

Patients randomized to the control group receive standard postoperative care.

The patient and surgical team will be able to know which arm of the study the patient is in based on documentation in the medical record of the administration of Entereg.

Patients in both groups will remain NPO until the return of bowel function, defined as passage of stool, decrease in nasogastric tube output. At this point, the nasogastric tube will be removed and a trial of oral diet will be attempted per surgeon's discretion.

Standard discharge criteria will be applied to all patients, including:
- Passage of stool
- Ability to tolerate solid food and to drink comfortably
- Adequate oral analgesia
- Patient's willingness to be discharged.

Data to be collected
The medical/surgical information below will be collected as part of this research study and is all information already available as part of the patients medical chart.
- Patient name, medical record number
- Past Medical History

- Past Surgical history
- Preoperative Medications (including steroids, anticoagulation, opioid use)
- Pre-operative Diagnosis
- Patient Demographics (age, gender, BMI, ASA score)
- Procedure performed
- Time of surgery
- Wound classification
- Estimated blood loss
- Intraoperative transfusion
- Intraoperative IV fluids given
- Conversion from laparoscopic to open procedure
- Stoma creation
- Time/day surgery to ileus
- Time from surgery to medication given
- Time from ileus diagnosis to medication given
- Was there return of bowel function (flatus or stool, solid or liquid, stoma output) prior to ileus
- Intra-abdominal infection/anastomotic leak
- Time/day of return of bowel function post ileus (flatus and stool- solid or liquid, and stoma function)
- Time/day of ability to tolerate oral diet (liquid and solid food)
- Nasogastric tube placement and daily output
- Duration of nasogastric tube
- Use and type of anti-emetics given
- Total number of Entereg doses given
- Post operative complications including reoperation
- Length of stay in hospital, defined as time from surgery to discharge
- 30-day readmissions

The above collected data will be put into a REDCap (Research Electronic Data Capture) database which is a secure web application for managing online surveys and databases. It allows the safe and secure storage of research data including storage of PHI HIPAA identifier fields.

Study Completion
Completion of participation in the study will be 30 days after the date of surgery. Any readmission up to 30 days post-operatively to the hospital as a direct result of their surgery will be followed. The patients will follow-up with the surgeon in the office in approximately 3-6 weeks, which is considered standard of care for all patients undergoing colorectal surgery and is not considered part of the research study. Any patient for whom follow-up documentation is missing or incomplete shall be contacted via telephone. The purpose of the call will be to simply determine return to function and outcome. Only a co-investigator shall contact the subject and will identify themselves at the beginning of the call. Any subject can reserve the right not to participate in the phone call interview; they would remain in the study.

Patient Withdrawal
A subject has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. The investigator and principal site also have the right to withdraw subjects from the study for the reasons listed below. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw or be withdrawn, reasonable efforts will be made to complete and report the observations as thoroughly as possible.

Subjects may be removed from the study, if any one or more of the following events occur:
- Serious Adverse Event
- Noncompliance
- Lost to follow-up
- Investigator/Principal site recommendation

- Withdrawal of consent
- Protocol Violation
- Intercurrent illness
- The investigator considers it in the patient's best interest to do so

This study is estimated to take 24 months for completion.

Statistical Plan

After recruitment of 71 patients, a safety monitoring board comprised of members of the University Hospitals Faculty will evaluate data and adverse events to ensure that there are not ongoing safety concerns that might call for early termination of the study.

Variables/Time Points of Interest

The following data will be recorded as described in the Study Procedures:

- Patient name, medical record number
- Past Medical History
- Past Surgical history
- Medications (including steroids, anticoagulation, opioid use)
- Pre-operative Diagnosis
- Patient Demographics (age, gender, BMI, ASA score)
- Procedure performed
- Time of surgery
- Wound classification
- Estimated blood loss
- Intraoperative transfusion
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- Time/day of ability to tolerate oral diet (liquid and solid food)
- Nasogastric tube placement and daily output
- Duration of nasogastric tube
- Total number of Entereg doses given
- Post operative complications including reoperation
- Length of stay in hospital, defined as time from surgery to discharge
- 30-day readmissions

Statistical Methods

The study co-investigators and research team will perform statistical analysis. Routine statistical analyses will be utilized for parametric and non-parametric datasets, as appropriate. Demographic data will be analyzed using students t-test or Fishers exact test as appropriate. Categorical data will be analyzed using X^2 analysis or Fishers exact test where applicable. Normally distributed data will be presented as means +/-SD of the mean, non-normally distributed data will be presented as medians +/- quartiles and categorical data will be presented as raw data and frequencies. A p value of < 0.05 will be considered statistically significant.

Power/Sample Size:

In our practice, patients undergoing open or laparoscopic colectomy without stoma creation who develop POI have a mean length of stay of 10.67 +/- 5.98 days compared to 4.86 days for patients who do not develop POI.

Using this information, to detect a significant decrease in length of stay by 3 days, with a 0.05 level of significance and a power of 80%, a total of 142 patients (71 patients per arm) are required.

Drug supplies (Entereg) for this study will be provided by Merck.

In the event that Merck is unable to provide drug supplies, the University Hospitals Case Medical Center Pharmacy will provide Entereg for this study.

The University Hospitals Case Medical Center Pharmacy will be responsible for distribution of drug in the treatment arm.

All adverse events will be reported per local IRB policy.

Reportable Problem: Any event which meets all three of the following criteria:

- Unexpected (in relation to the protocol and informed consent document),
- Related (in the investigator's opinion, the event has a 50% or greater chance of being related to the subject's participation in the study), and
- Gives evidence of new or increased risk to subject(s).

A reportable problem may include, but is not limited to, adverse events, protocol deviations, non-compliance, etc. Within 24 hours of knowledge of a reportable problem, the principal site must be notified. It is acceptable for the first notification to be a telephone conversation with the appropriate person at the principal site (leaving
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- Unexpected (in relation to the protocol and informed consent document),
- Related (in the investigator's opinion, the event has a 50% or greater chance of being related to the subject's participation in the study), and
- Gives evidence of new or increased risk to subject(s).

A reportable problem may include, but is not limited to, adverse events, protocol deviations, non-compliance, etc. Within 24 hours of knowledge of a reportable problem, the principal site must be notified. It is acceptable for the first notification to be a telephone conversation with the appropriate person at the principal site (leaving a message is not sufficient) as long as the appropriately-completed CRF is submitted in a timely manner following the call.

Adverse Event (AE): Any new, undesirable medical experience or worsening of a pre-existing condition which occurs during study procedure or follow-up. Any and all adverse events, regardless of seriousness, that meet the above definition of a reportable problem, will be reported to the principal site within the timeframes indicated above.
For reportable adverse events, the following will be determined and recorded on the adverse event case report form:

- Onset Date and Resolved Date (unless continuing)
- Intensity/Severity
- Discontinued due to AE
- Relationship to Drug/Procedure
- Action Taken
- Outcome

The following guideline is suggested in determining the severity of each adverse event in this study:

- Mild – event is noticeable but transient, requires no treatment and does not interfere with the subject's daily activities.

- Moderate – event causes a low level of inconvenience or discomfort to the subject and may partially interfere with daily activities, and may require treatment.
- Severe – event causes a high level of inconvenience or discomfort to the subject, interrupts daily activities and requires treatment.

Protocol Deviation: Deviations from the protocol (whether by the subject or investigative staff) that meet the criteria of a reportable problem (i.e. give evidence of new or increased risk to subject[s]) will be reported to the principal site within the timeframes indicated above. Protocol deviations that do not meet the criteria of a reportable problem should be reported to the principal site within 5 calendar days of knowledge of their occurrence. Emergent and purposeful deviations from the protocol to mitigate risk to subjects should be reported to the principal site within 24 hours of occurrence. Less urgent, purposeful deviations from the protocol should receive prospective approval by the principal site.

Non-compliance: Non-compliance with regulations must be reported to the principal site within 24 hours of occurrence, regardless of the event's meeting the criteria of a reportable problem defined above.

Additional items requiring prompt reporting to the principal site (within 24 hours):
- Any subject complaints indicating new or increased risk to subject(s)
- Breach of subject confidentiality
- Imprisonment of a study subject during study participation

Responsibility of Principal Investigator:
- Analysis of Adverse Events with respect to their clinical relevance and cause relation.
- Evaluation of necessary protocol amendments
- Provisional evaluation of the final results in the form of a written report, which will be the basis for an investigator reviewed publication.

Responsibility of Study Coordinator:
- The Study Coordinator will be responsible for monitoring the conduct of the study and data management at each site to ensure completeness and accuracy of data.
- The Study Coordinator will collect completed CRFs for analysis.
- The Study Coordinator will also be notified of any serious adverse event within 24 hours of knowledge of the event.

Responsibility of Study Group:
- The Study Group comprised of the PI, CO-Is and study coordinator will collectively review and analyze the data.
- Each member of the Study Group is responsible to conduct the Study in full compliance with the protocol and make sure that data collection is complete and accurate.

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A manuscript describing the results of this study will be submitted to a high impact journal. Possible journals include New England Journal of Medicine, Annals of Surgery, Journal of the American College of Surgeons, or Diseases of the Colon and Rectum.

A manuscript will be prepared and submitted at the completion of the study. Should results warrant, multiple publications may be produced.

Results and study abstract will be considered for submission to the national meeting of the American College of Surgeons, American Society of Colon and Rectal Surgeons, and/or the American Surgical Association.