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

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Background:

Most patients who undergo colorectal or small bowel resection (about 350,000 patients/year in the United States) will experience postoperative ileus, a temporary impairment of gastrointestinal function (8). POI is associated with increased morbidity, increased hospital length of stay (LOS), and increased health care costs (13). In most patients, LOS is typically determined by timing of GI recovery and POI has been shown to increase LOS by an average of 6 days with an annual cost of $1.46 billion (8). Currently, there is no specific treatment for or prevention of POI (8,16). Alvimopan is an oral, peripherally acting selective mu-opioid receptor antagonist that has been studied in patients undergoing abdominal and pelvic surgery, and was FDA approved in 2008 for short-term use to accelerate upper and lower gastrointestinal recovery in inpatients following segmental large or small bowel resection with primary anastomosis (8,14,15,16). Studies have demonstrated the effectiveness of Alvimopan in reducing time to return of bowel function, LOS and cost in abdominal surgery, however there have also been conflicting findings that have not observed these benefits in laparoscopic colorectal surgeries, have found no reduction in readmission rates or an increase in readmission rates, or have not found a reduction in cost (14,13,16,17,18). It is possible that the use of Alvimopan may be more effective in some populations than in others (i.e. low risk vs. high risk for POI, open vs. laparoscopic surgery) (13). The high cost of Alvimopan (currently $142.32/capsule) is of significant concern, and given prophylactically to all patients undergoing colorectal or small bowel resection may not be economically prudent as not all patients will develop POI or require treatment for POI (mild cases). This study aims to evaluate the cost effectiveness of Alvimopan as rescue therapy in patients undergoing colorectal or small bowel resection who develop POI, and its safety and effectiveness in reducing LOS and POI duration.

Hypothesis:

We hypothesize that the use of alvimopan as rescue therapy in patients undergoing colorectal and small bowel resection surgery who develop POI can shorten their duration of POI and hospital length of stay.

Objectives:

To perform a prospective RCT to evaluate the effect of alvimopan as rescue therapy compared to standard of care in reducing the duration of post-operative ileus and post-operative LOS after colorectal and small bowel resection surgery.

Protocol:

This will be a prospective randomized control trial with a total of 58 patients, 29 in each group. 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 Alvimopan as rescue therapy or to receive conservative standard care.

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 a maximum of 3 doses of Alvimopan 12mg orally, 12 hours apart. Alvimopan will be given from the time of diagnosis of postoperative ileus to the time of return of bowel function or the maximum 3 doses. Subsequent Alvimopan doses will be given if there is no return of bowel function or if symptoms of distension and/or nausea persist despite some return of bowel function.

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.

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 Alvimopan.

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.

Study Design:

This will be a prospective randomized control trial. 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 Alvimopan as rescue therapy or to receive conservative standard care.

Alvimopan will be prescribed as 1 dose PO with clamping of any NG tube if present for 30 minutes. A subsequent dose (up to a maximum of 3 doses) may be repeated 12 hours later if there has been no recovery of GI function.

Outcome: The primary outcome measure will be hospital length of stay after the diagnosis of POI (date of diagnosis until actual discharge). The secondary outcome measures will be: time to return of bowel function (date and time ileus identified to date and time of passing flatus, stool and tolerating diet), complications (serious adverse events and adverse events of interest 30 days postoperatively), number of re-operations (any reoperations within 30 days of surgery), number of readmissions (any readmissions within 30 days of surgery)

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. Patients with symptoms of bloating with or without nausea and vomiting, who require either:

i. Return to NPO status after initial diet attempts

ii. Undergo placement of a nasogastric tube

b. Patients with absence of passage of flatus or stool who are either

i. More than 5 days after open surgery without recovery of GI function

ii. More than 3 days after laparoscopic surgery or ileostomy closure without recovery of GI function

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 Alvimopan preoperatively.

2. Subjects that have already received scheduled peripherally acting mu-opioid receptor antagonists postoperatively.

3. Subjects that have taken therapeutic doses of opioids for more than 7 days immediately prior to surgery.

4. Subjects with severe hepatic impairment.

5. Subjects with end-stage renal disease.

6. Subjects who are pregnant.

7. Subjects who have undergone imaging suggesting a small bowel obstruction.

7. Subjects with a medical condition that may interfere with the use of the study medication Alvimopan.

8. Subjects who have a condition or general disability or infirmity that in the opinion of the investigator precludes further participation in the study

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.

A) Preoperative variables:

1. Patient name, medical record number

2. Past Medical History

3. Past Surgical history

4. Preoperative Medications (including steroids, anticoagulation, opioid use)

5. Pre-operative Diagnosis

6. Patient Demographics (age, gender, BMI, ASA score)

B) Intraoperative variables:

1. Procedure performed

1. Time of surgery

2. Wound classification

3. Estimated blood loss

4. Intraoperative transfusion

5. Intraoperative IV fluids given

6. Conversion from laparoscopic to open procedure

7. Stoma creation

C) Postoperative variables:

1. Time/day of diagnosis of ileus

2. Abdominal imaging demonstrating ileus if present

3. Time from surgery to medication given

4. Time from ileus diagnosis to medication given

5. Was there return of bowel function (flatus or stool, solid or liquid, stoma output) prior to ileus

6. Intra-abdominal infection/anastomotic leak

7. Time/day of return of bowel function post ileus (flatus and stool- solid or liquid, and stoma function)

8. Time/day of ability to tolerate oral diet (liquid and solid food)

9. Nasogastric tube placement and daily output

10. Duration of nasogastric tube

11. Use and type of anti-emetics given

12. Total number of Alvimopan doses given

13. Post operative complications including reoperation

14. Length of stay in hospital, defined as time from surgery to discharge

15. Length of POI, defined as time from diagnosis of POI until discharge

16. 30-day readmissions

Study Completion of participation in the study will be 30 days after the date of POI. 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.

Statistical Analysis

Planned Data Analysis:

Descriptive statistics will be computed for all variables including mean ± standard deviation or median [25^{th}, 75^{th} percentiles] for continuous factors and frequency (percent) for categorical variables. Univariate analyses will be conducted to compare the distribution of pre-op characteristics across treatment groups using t-test or Wilcoxon rank sum tests for continuous variables and Chi-square or Fisher's exact test for categorical variables.

The hospital length of stay after the diagnosis of POI and time to return of bowel function are defined as the interval between the day of POI diagnosis and day of actual discharge from the hospital, and the day of POI diagnosis and day of return of bowel function. T-test will be used to assess differences in the hospital length of stay after diagnosis of POI or time to return of bowel function across treatment groups. Multivariable linear regression will be conducted to adjust for baseline measurements as well as potential confounding variables such as gender, obesity, and operative time. Backwards variable selection will be used with a removal criteria of alpha > 0.1. When required, data will be transformed in order to meet normality assumptions.

For purposes of statistical analysis, a subset analysis may be done based on history of POI, type of operation, BMI, patients' gender, or other clinically significant co-factors. All data will be analyzed with the use of SAS (version 9.4, The SAS Institute, Cary, NC), SPSS statistical software (SPSS Inc., Chicago, IL), or R version 3.6.1 (www.R-project.org). A p-value <0.05 will be considered statistically significant.

Sample Size Calculations:

We conducted the sample size calculation using estimates of length of stay after the diagnosis of POI . We are assuming equal-sized treatment groups and alpha = 0.05.

We assumed that the average length of stay after the diagnosis of POI in no alvimopan group would be 4.25 days, and alvimopan group 2.75 days. Assuming a log-normal distribution, and co-efficient of variation of 0.6 based on prior data, there will be 80% power to detect decreases of a least 35% in length of stay after the diagnosis of POI in the Alvimopan group relative to the control group with 27 patients in each group, a total of 54 patients. Accounting for a dropout rate of about 5%, our enrollment goal will be 58 patients (29 per group).

Reporting of Results

Aggregate and anonymous, in text and table format, for publication in a medical journal.

Consent

A study coordinator will obtain informed consent from participating patients prior to Alvimopan administration. The coordinator will have HIPPA training, certification in human subject protection, and will be familiar with the research protocol. The study coordinator will explain to each participant the purpose of the study as well as give the patient the opportunity to opt out of participation. Consents will be kept in a room accessible only to qualified research personnel working in the CORS department.

Consents will be obtained prior to alvimopan administration. Patients will be offered participation in the study in a private clinic room. Patients will be offered to participate in the study post-operatively at the time of their post operative ileus diagnosis. Alvimopan is not part of the standard of care. It will be administered free of charge without extra financial charges to the enrolled patients.

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