

Outcomes of Alvimopan Use in Laparoscopic Intra-abdominal Surgery: A Retrospective Review

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ABSTRACT

Background: Postoperative ileus is a transient cessation of bowel motility, occurring after bowel resection, characterized by abdominal distension and pain, nausea, vomiting, and an accumulation of gas/fluids in the bowel. It is associated with a greater incidence of postoperative morbidity and increased length of stay or readmission. Alvimopan, a novel peripheral mu receptor antagonist, is indicated for preventing postoperative ileus in patients undergoing intra-abdominal surgery or bowel resection. The objective of this study was to assess the impact of alvimopan use in laparoscopic abdominal surgeries.

Objective: To assess alvimopan use's impact in laparoscopic abdominal surgeries.

Methods: A retrospective chart review was conducted of 84 patients who underwent laparoscopic procedures that received alvimopan (September 1, 2018 to October 31, 2018) and compared to patients that did not receive alvimopan (May 1, 2018 to June 30, 2018, due to a national shortage of the medication). The primary outcome was the rate of postoperative ileus. Secondary outcomes included rate of 30-day readmission, length of stay (LOS), postoperative opioid and laxative use, time to initiation of oral diet, and return of bowel function (ROBF) as demonstrated by recorded bowel movement.

Results: There was no statistical difference observed in primary outcome of postoperative ileus between alvimopan and no alvimopan groups (2.7% vs 4.3%, $p=1$). Secondary outcomes such as length of stay (5.4 days vs 5.4 days, $p=0.49$), length of postoperative stay (5 vs 4.9, $p=0.44$), days to oral diet (0.9 vs 0.4, $p=0.16$), time to BM (1.8 vs 2.2, $p=0.32$), and 30-day readmission were also similar between the two groups.

Conclusion: The similar outcome profiles in all primary and secondary outcomes do not support the use of alvimopan in the setting of laparoscopic intra-abdominal surgery.

Keywords: alvimopan, postoperative ileus, laparoscopic, intra-abdominal surgery

INTRODUCTION

Postoperative ileus (POI) is a temporary delay in gastrointestinal (GI) motility that occurs after abdominal surgery and prevents transit of intestinal contents or tolerance of dietary intake¹⁻². Symptoms include abdominal distension, pain, nausea and vomiting caused by an accumulation of gas and fluids in the bowel¹⁻². A common cause of POI is physical manipulation of the small and large intestines resulting in an inflammatory response and inhibition of normal neural signals for motility^{1-2,3}. Opioids, prescribed for management postoperative pain, can exacerbate the condition^{1-2,3}. POI is associated with a greater incidence of postoperative morbidity and is a common reason for an increased hospital length of stay (LOS) as well as 30-day readmission¹⁻⁴. Various strategies have been implemented in attempts to minimize the incidence and duration of postoperative ileus such as providing epidural anesthesia, performing less invasive surgeries such as laparoscopy, and establishing enhanced recovery protocols through multi-modal pain control, early ambulation, and early introduction of an oral diet^{1,2,5,6}.

Alvimopan (Entereg) is an oral mu-opioid receptor antagonist used to prevent the opioid side effect of slowed GI motility following partial large-bowel or small-bowel resection with primary anastomosis^{1-3,7}. Working primarily in the periphery on the mu-receptors in the GI tract, alvimopan can reduce both the incidence and duration of postoperative ileus^{1-3,7}. Since alvimopan does not cross the blood-brain barrier, analgesic activity mediated by mu-opioid receptors in the central nervous system remains unaffected^{1-2,3}. Alvimopan is commonly used to accelerate GI recovery in patients undergoing laparotomy for bowel resection. Its benefits in open-approach abdominal surgeries include acceleration of return of GI function after surgery and reduction in patient's hospital LOS^{7,8}. Of note, patients undergoing laparoscopic procedures were excluded from several trials and its benefits in this population remains controversial^{3,9}. Recent retrospective cohort studies have indicated insufficient or no significant benefit to the use of alvimopan in laparoscopic procedures⁴. In this study, we investigated the clinical benefit of alvimopan use in patients undergoing laparoscopic intra-abdominal surgery.

METHODS

Study Design and Measured Endpoints

This was an observational study of all patients who underwent laparoscopic intra-abdominal procedures that received alvimopan (September 1, 2018 to October 31, 2018) compared to patients that did not receive alvimopan (May 1, 2018 to June 30, 2018) at Anne Arundel Medical Center (AAMC), a 389-bed regional health system located in Annapolis, Maryland. Patients

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did not receive alvimopan during the aforementioned time period due to a national drug shortage. Exclusion criteria included open procedures or conversion to open procedure, as well as emergent cases, where patients did not receive a preoperative dose of alvimopan, as per manufacturer recommended dosing standard. No-alvimopan group patients were captured by screening for patients that had qualifying procedures by the same surgery group. EPIC electronic medical record was utilized for retrospective review, and data collection included patient age, gender, Charlson Comorbidity Index, intensive care unit (ICU) admission, total alvimopan doses, hospital and post-operative length of stay, post-operative days till first bowel movement, post-operative days till oral diet, development of ileus, 30-day readmission, and other clinical variables. AAMC Institutional Review Board approved this study protocol in June 18, 2020.

Measured Endpoints and Clinical Assessment

The primary endpoint measured was the development of postoperative ileus. Secondary endpoints included rate of 30-day readmission, hospital and post-operative length of stay, postoperative opioid and laxative use, and time to initiation of oral diet.

Statistical Analysis

For comparison of the categorical variable between the two groups, the chi-square test or Fisher's exact test was used for smaller samples where appropriate. The student's t-test was used for continuous data, such as age, LOS, and times to PO diet or bowel function. Online calculators from socsistatistics.com and graphpad.com were utilized to perform statistical analysis. A p-value <0.05 was deemed statistically significant.

RESULTS

Patients

A total of 84 patients were identified during the study period, with 37 in the alvimopan group and 47 in the no-alvimopan group included in the final analysis (Figure 1). Baseline demographics are listed in Table 1, with indications for surgery presented in Table 2. Age and gender of patient populations in both groups were similar. There was no difference between the two groups in the number of patients requiring an ICU stay during admission. In addition, Charlson Comorbidity Index was similar between the alvimopan and no-alvimopan groups. Surgical need (elective vs. non-elective) was also similar between the two groups.

Primary, secondary, and other pre-defined clinical endpoints are summarized in Table 3. There was no statistically significant difference in the rate of postoperative ileus (2.7% vs. 4.3%, $p=1$) between the alvimopan and no-alvimopan groups. The rate of 30-day readmission rate for patients in the alvimopan group was also comparable to those who did not receive alvimopan (5.4% vs. 4.3%, $p=1$). The patient LOS, as well as the postoperative LOS were not statistically significant between the two study populations. Lastly, there was no statistically

significant difference between the rate of opioids, laxatives, and anti-emetics use between the alvimopan and no-alvimopan groups.

DISCUSSION

Postoperative ileus (POI) following intra-abdominal surgeries can be a significant barrier to recovery, leading to delayed return of bowel function (ROBF), increased length of stay (LOS), along with an increased cost associated with that longer hospital admission. Various strategies have been implemented in an effort to reduce the incidence of POI. Using minimally invasive laparoscopic techniques, implementing an enhanced recovery pathway (ERP), and using alvimopan have all been utilized. In addition, bowel regimens including stimulant laxatives may also assist with reducing time to bowel movement.

Historically, there has been a dearth of evidence evaluating the benefits of alvimopan in laparoscopic abdominal procedures utilizing an ERP, as much of the data from the initial clinical trials excluded such procedures^{1,2,3}. Our retrospective review sought to determine the impact of the use of alvimopan in the aforementioned setting, as currently alvimopan is used as standard of care in all abdominal surgeries at our institution. Our study results are consistent with others in literature that have shown no statistically significant benefit of alvimopan use in reducing the incidence of POI, postoperative LOS, and 30-day readmission rates in patients undergoing laparoscopic abdominal procedures. Tucker et al. showed comparable rates of post-operative ileus in alvimopan and no alvimopan groups in patients undergoing elective colon/rectal procedures (33.3% vs. 32.5%, $p = 0.45$). In addition, post-operative length of stay (6.68 days vs. 5.85 days, $p=0.26$), and 30-day readmission (17.7% vs. 18.5%, $p = 0.077$) were not statistically significant¹⁰. Keller et al. evaluated the benefit of alvimopan in laparoscopic colorectal surgery with an ERP and concluded that alvimopan added no clinical benefit in patient outcomes in laparoscopic colorectal surgery with an ERP¹¹. Similarly, our study found no statistically significant difference in postoperative days until oral diet initiation, and postoperative days until first bowel movement as markers of ROBF.

Our study findings can be attributed to less pain, lower opioid requirements, and a shorter recovery time at baseline seen in patients who undergo elective laparoscopic procedures. The implementation of an ERP, initiated early in a patient's hospital course, appears to have a positive impact on reducing POI, LOS, ROBF. Key elements include rapid patient ambulation, early introduction of an oral diet, and minimization of opioid use with a multi-modal pain approach to postoperative pain control. This synergistic approach may negate the need for alvimopan. Lastly, reducing or eliminating the use of alvimopan in this setting could have significant cost savings, approximately \$177,000 per year at acquisition cost of \$165 per dose. This review helps establish alvimopan use rationale may be limited

to open procedures, with minimal benefit shown in laparoscopic procedures.

This study is not without limitations, which include its single-center retrospective design and small sample size, making our conclusions less generalizable to hospitals with dissimilar patient populations, such as those with higher rates of non-elective surgeries and those with higher incidence of comorbidities. The limited number of surgeons performing the applicable procedures at our institution may also limit the extrapolation of our conclusions to other institutions. Additional limitations include only inclusion of patients able to receive the preoperative dose of alvimopan being included in our data set, limiting the population to elective procedures. Moreover, the definitions of postoperative ileus vary across literature, defined as resolution of gastrointestinal function ranging from 2 to 7 days, and ranging from 10 to 30% following abdominal surgeries¹³. The presence of postoperative ileus in our study was based upon interventions required for the condition, or on its mention in review of progress notes written by the surgical service. Lastly, more patients in the alvimopan group had cancer-related indications for laparoscopic surgery, which could impact some of the endpoints evaluated in this study as they are more prone to adverse surgical outcomes.

In conclusion, our study findings highlight that alvimopan is not associated with a reduction in the incidence of POI, 30-day readmission rates, and hospital and post-operative LOS. Prospective, multicenter, randomized-controlled trials are needed to determine whether alvimopan has any impact on improving clinical outcomes in patients undergoing laparoscopic intra-abdominal surgery as a part of ERP.

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Conflict of Interest: We declare no conflicts of interest or financial interests that the authors or members of their immediate families have in any product or service discussed in the manuscript, including grants (pending or received), employment, gifts, stock holdings or options, honoraria, consultancies, expert testimony, patents and royalties.

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Figure 1. Flowchart of study patients.

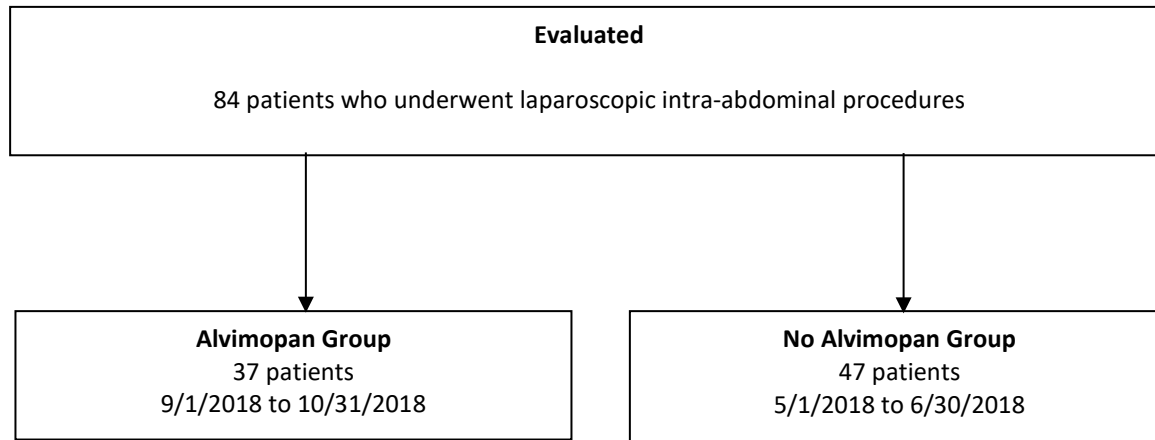


Table 1. Baseline patient demographics and clinical conditions

Characteristic [†]	Alvimopan Group (n=37)	No Alvimopan Group (n=47)	P-value
Age, years, median (IQR)	62 (51-71)	65 (57-74.5)	0.12
Male	18 (48.6%)	16 (34%)	0.18
Charlson Comorbidity Index, median (IQR)	3 (1-5)	3 (2-5)	0.77
Elective surgery	37 (100%)	42 (89.4%)	0.06
ICU stay	2 (5.4%)	2 (4.3%)	1

[†]Data are presented as number (percent) of patients, unless specified otherwise.

Table 2. Indications for laparoscopic surgery

Indication [†]	Alvimopan Group (n=37)	No Alvimopan Group (n=47)	p-value
Anatomical	5	2	p=0.16
Appendicitis	13	10	p=0.29
Cancer-related	42	18	p=0.002
Cholecystitis	4	5	p=0.98
Diverticulitis	23	16	p=0.12
Hernia	8	16	p=0.35
Intestinal obstruction	5	3	p=0.32
Other	12	11	p=0.49

[†]Patients with multiple indications included in individual categories

Table 3. Primary, Secondary, and other pre-defined endpoints

Endpoint [†]	Alvimopan (n=37)	No Alvimopan (n=47)	P-value
Postoperative ileus, n (%)	1 (2.7%)	2 (4.3%)	1
LOS, days (IQR)	5.4 (2-6)	5.4 (3-5)	0.49
Post-operative LOS, days (IQR)	5 (2-5)	4.9 (3-5)	0.44
30-day readmission, n (%)	2 (5.4%)	2 (4.3%)	1
Postoperative opioid use, n (%)	31 (83.8%)	37 (78.7%)	0.56
Time to oral diet, days (IQR)	0.9 (0-1)	0.4 (0-1)	0.16
Time to bowel movement, days (IQR)	1.8 (1-2.5)	2.2 (1-2)	0.32
Use of Laxatives, n (%)	1 (2.7%)	5 (10.6%)	0.23

[†]Data are presented as median (IQR), unless specified otherwise.