

Alvimopan Provides Additional Improvement in Outcomes and Cost Savings in Enhanced Recovery Colorectal Surgery

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Objective: To examine the impact of alvimopan on outcomes and costs in a rigorous enhanced recovery colorectal surgery protocol.

Background: Postoperative ileus remains a major source of morbidity and costs in colorectal surgery. Alvimopan has been shown to reduce incidence of postoperative ileus in enhanced recovery colorectal surgery; however, data are equivocal regarding its benefit in reducing length of stay and costs.

Methods: Patients undergoing major elective enhanced recovery colorectal surgery were identified from a prospectively-collected database (2010–2013). Multivariable analyses were employed to compare outcomes and hospital costs among patients who had alvimopan versus no alvimopan by adjusting for demographic, clinical, and treatment characteristics.

Results: A total of 660 patients were included; 197 patients received alvimopan and 463 patients had no alvimopan. In unadjusted analysis, the alvimopan group had a faster return of bowel function, shorter length of stay, and lower rates of ileus, Foley re-insertion, and urinary tract infection (all $P < 0.01$). After adjustment, alvimopan was associated with a faster return of bowel function by 0.6 day ($P = 0.0006$), and lower incidence of postoperative ileus (odds ratio 0.23, $P = 0.0002$). With adjustment, alvimopan was associated with a shorter length of stay by 1.6 days ($P = 0.002$), and a hospital cost savings of \$1492 per patient ($P = 0.01$).

Conclusions: Alvimopan administration as an element of enhanced recovery colorectal surgery is associated with faster return of bowel function, lower incidence of postoperative ileus, shorter hospitalization, and a significant cost savings. These results suggest that alvimopan is cost-effective in the setting of enhanced recovery colorectal surgery protocols, and should therefore be considered in these programs.

Keywords: alvimopan, colorectal surgery, entereg, enhanced recovery after surgery

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Postoperative ileus is a frequent occurrence after colorectal surgery, representing a major source of postoperative morbidity, prolonged hospitalization, increased resource use, and higher costs.^{1–3} Although the pathogenesis of postoperative ileus is multifactorial, endogenous and exogenous opioids play a central role in the development of postoperative ileus. Endogenous opioids released in response to stress of surgery and exogenous opioids administered for pain control can activate mu-opioid receptors in the gastrointestinal tract, resulting in decreased gastrointestinal motility.^{4–6}

Enhanced recovery colorectal surgery programs have been implemented to optimize perioperative care and reduce complications such as postoperative ileus.^{7,8} These programs employ a multimodal approach aiming at reduction of perioperative stress, through patient care elements, including utilization of minimally invasive techniques, adjunct nonopioids medications, early postoperative feeding and early mobilization. Accumulating evidence suggest that implementation of enhanced recovery protocols in colorectal surgery is associated with earlier recovery of gastrointestinal function with significant reduction in incidence of postoperative ileus and hospital length of stay by 2 days for both open and laparoscopic procedures.^{9–13}

Alvimopan is a peripherally acting mu-opioid receptor antagonist that blocks the gastrointestinal effects of opioids while preserving the central analgesic effect of administered opioids. Alvimopan has been shown to prevent postoperative ileus and promote recovery of gastrointestinal function after bowel resection with primary anastomosis in up to half of the patients.^{14,15} Despite these proven benefits of alvimopan in bowel surgery in general, its utility in the setting of enhanced recovery colorectal surgery remains to be seen. Colorectal surgery patients on enhanced recovery protocols are well optimized with care plans created to minimize physiologic causes of ileus. Opinions that alvimopan may not provide significant improvement to this optimized population have been reported.¹⁶ Further, concerns were also raised with regard to the cost of alvimopan, with an estimated cost of >\$1000 for a 7-day course. In the absence of a clinically significant improvement provided by alvimopan, use of this medication may not be cost-effective.

Published data examining the role of alvimopan in the setting of enhanced recovery colorectal surgery protocols are inconsistent in determining the effect of alvimopan on hospital length of stay and costs.^{17–19} Generally, these studies were limited by sample size, which precluded adequate multivariable adjustment for important confounders. Therefore, we sought to examine the impact of alvimopan on clinical outcomes, hospital length of stay, and costs in a large cohort of patients undergoing major enhanced recovery colorectal surgery.

METHODS

Data Source

Patients undergoing major elective colorectal surgery under enhanced recovery protocol at Duke University Medical Center between February 2010 and May 2013 were identified from a prospectively collected database. Data for all patients undergoing major elective colorectal surgery under enhanced recovery protocol are recorded prospectively by a trained surgical reviewer. Data accuracy is ensured through internal auditing. Patients undergoing the following procedures were included in the study: segmental colectomy, total abdominal colectomy, total abdominal colectomy

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with ileostomy, total proctocolectomy with ileoanal pouch, low anterior resection, and abdominoperineal resection. All procedures were elective and performed by 1 of 3 board-certified colorectal surgeons.

Patient age, sex, race, body mass index (BMI), American Society of Anesthesiologists (ASA) score, diagnosis, year of the procedure, history of opioid use, use of thoracic epidural analgesia and laparoscopy, and extent of resection were extracted from the dataset. Data on perioperative outcomes, such as time to return to bowel function, postoperative ileus, postoperative urinary tract infection, length of hospital stay, and 30-day readmission were obtained from the dataset. Postoperative ileus was defined as re-insertion of nasogastric tube in the absence of other indications, such as mechanical obstruction and intubation. Length of stay was calculated from the day of the procedure to discharge. Variable direct costs for the index admission were obtained from our finance department. Variable direct costs account for costs incurred during a hospital stay related to care provided to the patient but exclude utilities and physician fees. Variable direct costs were grouped into: (1) surgery costs (eg, operating room time and equipment), (2) pharmacy-related costs (eg, pharmaceutical agents), (3) diagnostic costs (eg, laboratory and radiology tests), (4) patient care costs (eg, nursing), and (4) total hospital costs.

Enhanced Recovery Colorectal Surgery Protocol

The Duke Enhanced Recovery Program was initially based on the principles presented by the Enhanced Recovery After Surgery (ERAS) Society.^{13,20,21} Modifications with inclusion of the anesthetic components detailed in the NICE program from the UK and other specific to the care practices of the US have been incorporated.²² The essential Duke protocol and reported improvements in outcomes has been previously published.¹³ Before surgery, patients are educated on the components of the program and on expectations with regard to the patient's role. Preoperative fasting is minimized; clear liquids are allowed up to 2 hours before surgery, and a carbohydrate-rich beverage is prescribed at 3 hours before anesthesia induction time.²³ All patients receive preoperative antibiotic and thromboembolic prophylaxis. Multimodal pain management is begun in the preoperative space, as is multimodal prevention of postoperative nausea and vomiting.²⁴ Intraoperatively, goal-directed fluid administration is employed with the use of esophageal Doppler or noninvasive hemodynamic monitoring devices.²⁵ Epidural analgesia and minimally invasive surgical approach are used when appropriate. Postoperatively, patients are immediately allowed a diet and are encouraged to ambulate on day of surgery. Intravenous fluid and opioids are minimized by encouraging oral hydration and use of adjunct analgesics, respectively. Then patient is deemed suitable for discharge when oral intake is adequate to maintain hydration, and pain control is adequate with an oral regimen. Before discharge, the patient is counseled with postdischarge expectations and understanding of issues that would require contacting the surgical team and/or presentation to the emergency department. Finally, in addition to receiving postoperative venous thromboembolism (VTE) prophylaxis when in the hospital, the patient is prescribed VTE prophylaxis after discharge.

Alvimopan was not part of our early institutional enhanced recovery protocol, and its use was based on surgeon preference and/or availability. When prescribed, a single dose of alvimopan 12 mg orally was given preoperatively, followed by a 12 mg orally every 12 hours until first bowel movement or for a maximum of 7 days. Patients who received at least a preoperative dose and 1 dose postoperatively were included. Those who had only 1 dose of the medication were excluded ($n = 16$ patients). Data on timing and dosage of alvimopan administration were confirmed from the nursing medication administration sheets.

Statistical Analysis

The cohort was analyzed into 2 groups—patients who had alvimopan treatment and those who did not receive alvimopan (control). Patient demographic, clinical, and other treatment characteristics were compared between the alvimopan treatment versus control groups using the Fisher's exact/ χ^2 and Kruskal–Wallis tests.

Short-term outcomes were compared between alvimopan versus control using multivariable regression analyses by adjusting for patient age, sex, race, BMI, ASA score, diagnosis, history of opioid use, year of procedure, extent of surgery, use of laparoscopy and epidural, and the operating surgeon. Multivariable logistic regression modeling was used to analyze dichotomous outcome variables such as rates of postoperative ileus and 30-day readmission. Multivariable linear regression modeling was used to examine time to return of bowel function, length of stay, and hospital costs. After adjustment for the covariates, the predicted means of the outcomes based on the model were obtained for the 2 groups. When the log transformation of the outcome was used to model the data, the predicted means were exponentiated to obtain predicted values. The level of statistical significance was set a priori at a two-sided P value of <0.05 . Statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 660 patients underwent major elective colorectal resections between 2010 and 2013 at our institution. Of these, 197 patients received alvimopan treatment, and 463 were not treated with alvimopan. Patient age, sex, race, BMI, and ASA scores were not different between the 2 groups. Indications for surgery were similar between the 2 groups (Table 1). Compared with control, patients treated with alvimopan were more often to undergo a segmental colectomy (61% vs 51%, $P = 0.048$) and a laparoscopic approach (64% vs 56%, $P = 0.047$).

Short-term Outcomes

Median number of alvimopan doses given was 6 doses per patient (interquartile range 4–8 doses). In unadjusted analysis, patients treated with alvimopan versus control had lower rates of postoperative ileus (5% vs 16%, $P < 0.0001$), re-insertion of indwelling Foley catheter (7% vs 14%, $P = 0.008$), and postoperative urinary tract infection (5% vs 12%, $P = 0.005$). Compared with control, the alvimopan group had a shorter hospital length of stay (median 4 vs 5 days, $P = 0.0002$) and a similar rate of 30-day readmissions (10% vs 12%, $P = 0.35$) (Table 2).

After adjustment for patient's demographics, ASA score, diagnosis, year of surgery, extent of surgery, and use of epidural and laparoscopy, alvimopan treatment versus control was associated with a significantly faster return of bowel function (-0.6 days, $P = 0.0006$), lower likelihood of postoperative ileus [odds ratio (OR) 0.23, 95% confidence interval (CI) 0.11–0.50, $P = 0.0002$], and shorter hospital length of stay (-1.6 days, $P = 0.002$) (Table 3).

Hospital Costs

Compared with control, patients treated with alvimopan had lower patient care costs (median \$1890 vs \$2349, $P = 0.0002$), pharmacy costs (\$722 vs \$786, $P = 0.04$), and total variable direct hospital costs (median \$8749 vs \$9507, $P = 0.02$) (Table 4). After adjustment for patient demographics, ASA score, diagnosis, year of surgery, extent of surgery, use of laparoscopy or epidural, and operating surgeon, alvimopan treatment versus control was associated with reduced patient care costs ($-\$1261$, $P < 0.0001$), pharmacy costs ($-\$187$, $P = 0.03$), and total variable direct hospital costs ($-\$1492$, $P = 0.01$); operative costs were similar between the 2 groups ($P = 0.57$) (Fig. 1).

TABLE 1. Patient Demographic, Clinical, and Treatment Characteristics by Alvimopan Treatment

	Control (N = 463)	Alvimopan (N = 197)	P Value
Patient age (years, mean ± SD)	58 ± 15	59 ± 15	0.49
Male sex	231 (50%)	111 (56%)	0.15
Race			0.70
White	347 (75%)	143 (73%)	
Black	99 (21%)	48 (24%)	
Others	16 (4%)	6 (3%)	
BMI (mean ± SD)	29 ± 6	28 ± 6	0.55
ASA score			0.33
1	23 (5%)	6 (3%)	
2	148 (32%)	72 (37%)	
≥3	292 (63%)	119 (60%)	
Diagnosis			0.41
Benign	94 (20%)	44 (22.3%)	
Inflammatory	64 (14%)	20 (10.2%)	
Neoplastic	305 (66%)	133 (67.5%)	
Year of procedure			<0.0001
2010	200 (43%)	0	
2011	149 (32%)	32 (16%)	
2012	93 (20%)	107 (54%)	
2013	21 (5%)	58 (29%)	
History of opioid use	30 (6%)	9 (5%)	0.37
Epidural placement	416 (90%)	175 (89%)	0.79
Procedure			0.05
Segmental colectomy	236 (51%)	121 (61%)	
Total colectomy	23 (5%)	9 (5%)	
Total colectomy with ileostomy	18 (4%)	5 (3%)	
Total proctocolectomy with ileoanal pouch	35 (8%)	9 (5%)	
Low anterior resection	124 (27%)	36 (18%)	
Abdominoperineal resection	27 (6%)	17 (9%)	
Laparoscopic approach	258 (56%)	126 (64%)	0.047

ASA indicates American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

Subset Analysis

Patients with prior history of opioid use were included in the analysis. Given that alvimopan is contraindicated in a subset of patients with history of opioid use (patients taking therapeutic doses of opioids for more than 7 consecutive days immediately before taking alvimopan), we performed a sensitivity analysis in which we excluded patients with a prior history of opioid use. After adjustment for patient, clinical, and treatment characteristics, use of alvimopan remained significantly associated with shorter hospital length of stay (adjusted means 8.5 vs 9.8 days, $P=0.008$) and reduced hospital costs (adjusted means \$14,998 vs \$16,213, $P=0.03$).

DISCUSSION

This large, single-institution study examined the impact of alvimopan treatment on clinical outcomes and hospital costs in 660 patients undergoing major elective colorectal surgery under a

rigorous enhanced recovery protocol. After adjustment for patient demographic, clinical, disease, and treatment characteristics, alvimopan use was associated with a significantly faster return of bowel function and fewer incidences of postoperative ileus, indwelling Foley catheter re-insertion, and postoperative urinary tract infection. Hospital length of stay was significantly shorter in the alvimopan group (−1.6 days, $P=0.002$), without an increase in 30-day readmission rate ($P=0.69$). With adjustment, alvimopan treatment was associated with a significant reduction in patient care costs (−\$1261, $P<0.001$) and even pharmacy-related costs (−\$187, $P=0.03$), amounting a total of hospital cost savings of \$1492 per patient. This suggests that alvimopan is cost-effective in the setting of enhanced recovery protocols, offsetting the cost of this medication by a large margin. Therefore, adding alvimopan to enhanced recovery colorectal surgery programs may provide significant improvement in outcomes and hospital cost savings.

TABLE 2. Unadjusted Short-term Outcomes in Patients Treated With Alvimopan Versus Control

Outcomes	Control (N = 463)	Alvimopan (N = 197)	P Value
EBL [ml, median (IQR)]	113 (50–300)	100 (50–300)	0.14
ROBF [days, median (IQR)]	2 (1–3)	2 (1–2)	0.03
Postoperative ileus	74 (16%)	9 (5%)	<0.0001
Foley removal [days, median (IQR)]	2 (2–3)	2 (2–3)	0.94
Foley catheter re-insertion	64 (14%)	13 (7%)	0.008
Urinary tract infection	57 (12%)	10 (5%)	0.005
Length of stay [days, median (IQR)]	5 (4–7)	4 (3–6)	0.0002
30-day readmission	57 (12%)	19 (10%)	0.35

EBL indicates estimated blood loss; IQR, interquartile range; POD, postoperative day; ROBF, return of bowel function.

TABLE 3. Summary of Multivariable Short-term Outcomes Analyses Examining the Adjusted Association of Each Outcome With Alvimopan Treatment Versus Control

	Mean Difference	OR (95 CI)	P Value
Return of bowel function	-0.6 days	-	0.0006
Postoperative ileus	-	0.23 (0.11–0.50)	0.0002
Length of hospital stay	-1.6 days	-	0.002
30-day readmission	-	0.89 (0.50–1.58)	0.69

Outcomes were examined in different multivariable models with adjustment for patient age, sex, race, BMI, ASA scores, diagnosis, extent of surgery, use of laparoscopy and epidural, and operating surgeon.

CI indicates confidence interval; OR, odds ratio.

TABLE 4. Unadjusted Costs in Patients Treated With Alvimopan Versus Control

	Control (N = 463)	Alvimopan (N = 197)	P Value
Patient care cost	\$2349 (1565–3873)	\$1890 (1339–2597)	0.0002
Diagnostic cost	\$358 (209–789)	\$396 (168–869)	0.85
Operative cost	\$5507 (4593–6762)	\$5558 (4762–6592)	0.77
Pharmacy cost	\$786 (573–1164)	\$722 (568–952)	0.04
Total hospital costs	\$9507 (7658–12,171)	\$8749 (7594–10,853)	0.02

Costs data are presented as median (interquartile range).

Although there are robust randomized and retrospective data that established the beneficial effect of alvimopan on reducing postoperative ileus, hospitalization, and hospital costs after bowel resection in general,^{14,15,26–29} these beneficial effects of alvimopan may not be generalizable in a setting of enhanced recovery colorectal surgery protocol. Patients undergoing colorectal surgery under enhanced recovery protocols are well optimized with a significantly decreased postoperative morbidity and length of hospitalization. Therefore, alvimopan may not add a clinically significant improvement in these already well-optimized patients. Published data examining the role of alvimopan in the setting of enhanced recovery colorectal surgery have largely shown its ability to decrease

postoperative ileus. However, the reported effect of alvimopan on hospital length of stay and costs has been inconsistent.^{17–19} Some of these studies are limited by small sample size, precluding adequate adjustment for important confounders, such as comorbidities and extent of resection. Kelley et al¹⁹ examined the effect of alvimopan in 90 patients who had minimally invasive colorectal surgery under enhanced recovery protocol at a single institution. The study included 26 patients who were treated with alvimopan and 64 patients in the control group. In unadjusted analysis, the alvimopan group had a significantly shorter time to tolerance of soft diet (median 2 days vs 3 days, $P=0.02$) and return of bowel function (median 1 day vs 2 days, $P=0.003$); hospital length of stay was significantly shorter in the alvimopan group (median 3 days vs 4 days, $P=0.02$). In a larger single-institutional study, Obokhare et al¹⁸ examined the effect of alvimopan on 100 patients who had laparoscopic colectomy against a similar number of a matched control. The patients were matched by age, sex, and diagnosis. They found that patients on alvimopan were significantly less likely to develop postoperative ileus (4% vs 12%, $P=0.04$); however, length of stay was similar between the 2 groups (3.6 days vs 3.8 days, $P=0.84$).

In our study, the use of alvimopan use was independently associated with faster return of bowel function, fewer incidences of postoperative ileus, and shorter hospitalization by 1.6 days. Additionally, our study included patients who had open and laparoscopic colorectal resections; multivariable adjustment controlled for possible effects of laparoscopic approach on outcomes of interest. The large sample size allowed adequate control for other important confounders, such as patients' demographics, comorbidities (represented by ASA score), history of opioid use, diagnosis, extent of resection, use of epidural analgesia, and operating surgeon—a limitation of previous studies.

Our demonstrated benefit of alvimopan on reducing incidence of postoperative ileus and hospital length of stay are consistent with previous data from randomized clinical trials that examined the effect of alvimopan in patients undergoing bowel resection. In a pooled analysis of phase III randomized clinical trials, Delaney et al³⁰ demonstrated that alvimopan versus control was associated with significant reduction in rate of prolonged hospital length of stay (7% vs 14%, $P=0.002$). Our study suggests that the benefit of alvimopan

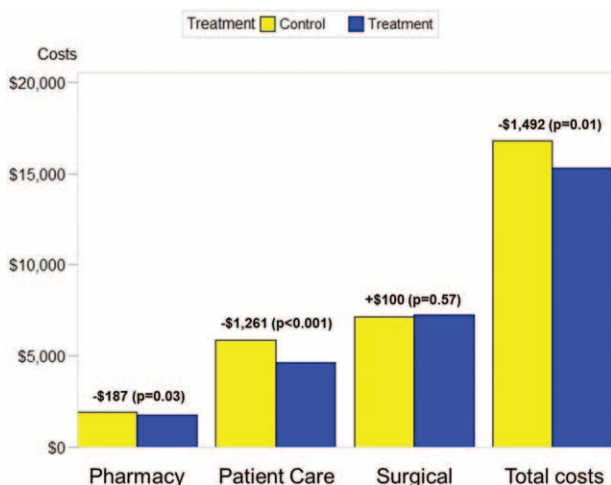


FIGURE 1. Adjusted analyses examining association of alvimopan treatment versus control and hospital costs. Data are presented as adjusted mean differences. Each cost measure was examined in a separate multivariable model with adjustment for patient age, sex, race, BMI, ASA scores, diagnosis, history of opioid use, year of procedure, extent of surgery, use of laparoscopy and epidural, and operating surgeon.

in these trials can be extended to enhanced recovery colorectal surgery protocols.

In the current study, patients treated with alvimopan had a lower incidence of postoperative urinary tract infection. This is likely explained by the higher incidence of re-insertion of indwelling Foley catheters in the control group. Patients with postoperative ileus are dependent on intravenous hydration and urine output monitoring. Prior studies have established the association between postoperative ileus and urinary tract infection in patients undergoing colorectal surgery.³¹

Limited data exist examining the cost-effectiveness of alvimopan in the setting of enhanced recovery colorectal surgery. In a single-institution study of 90 patients undergoing minimally invasive colectomy, hospital costs (reported as percentages) were examined among patients who received alvimopan ($n=26$) versus those who did not receive alvimopan ($n=64$). In unadjusted analysis, patient care costs were significantly decreased in the alvimopan group (42% vs 58%, $P=0.02$). Similarly, combined hospital costs were lower in the alvimopan group, although it did not reach statistical significance (46% vs 54%, $P=0.09$).¹⁹ With a large sample size, permitting multivariable adjustment for confounders, we demonstrated that alvimopan was associated with a statistically significant hospital cost savings of \$1492 per patient. This cost savings were largely driven by reduction in patient care costs ($-\$1261$), which is likely a reflection of the lower incidence of postoperative ileus and shorter length of hospitalization. In a large population-based study of 17,876 patients undergoing colectomy, postoperative ileus was associated with a 1.6 days increase in hospital length of stay and a higher hospital cost of \$1461 per patient.³ It is also important to highlight that despite the high cost of alvimopan, pharmacy-related costs were reduced, underscoring the cost-effectiveness of this expensive medication. The decrease in pharmacy-related costs is likely driven by the reduction in incidence of postoperative ileus, and the less use of medications afforded by the shorter hospital length of stay.

Limitations to our study include those inherent to retrospective studies, such as the potential for selection bias. Expecting this issue, we carefully adjusted for possible patient demographic and clinical confounders. There could also be other unmeasured confounders that contributed to the reported effect of alvimopan; however, data utilized in this analysis were granular, permitting to adjust for known confounders reported in the literature. Although data on history of opioid use were not granular enough to definitively determine appropriateness of alvimopan treatment, we have performed a subset analysis in which we excluded patients with a history of preoperative opioid use. After exclusion of this group of patients and with adjustment, alvimopan use remained significantly associated with shorter length of stay and reduced hospital costs. A portion of our control group was historical, from a year behind. However, year of the procedure was controlled for in our multivariable analyses.

CONCLUSIONS

This large, single institutional study provides valuable information regarding the effect of alvimopan on hospital length of stay and costs in the setting of enhanced recovery colorectal surgery protocol. We attempted to address some of the methodological limitations of the existing literature by adjusting for significant patient demographic, medical, and surgical confounders, and reported actual hospital costs. We demonstrated that the addition of alvimopan to an enhanced recovery colorectal surgery protocol is associated with reduction in hospital length of stay and a significant cost savings of \$1492 per patients. As our health care system is becoming more cost-conscious and quality-focused, utilization of

alvimopan can provide an opportunity for significant cost savings. This is particularly important with knowing that there are more than 300,000 colorectal operations performed annually in the US. A cost saving of \$1492 per patient could translate into a significant cost savings to the health care system. As such, we believe that alvimopan should be considered as a part of enhanced recovery colorectal surgery programs.

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