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RESEARCH ARTICLE

A Retrospective Study of Patients Undergoing Gastrointestinal Surgery with or without Receiving Alvimopan: Comparing Length of Stay and Total Direct Cost

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ABSTRACT

Objective: Alvimopan (Entereg®) has been shown to accelerate the recovery time of upper and lower gastrointestinal (GI) system following partial large or small bowel resection with primary anastomosis.

Alvimopan acquisition cost can increase health care costs. The purpose of this study is to assess the effectiveness of alvimopan reducing the length of stay (LOS) and total direct cost in patients undergoing gastrointestinal surgery.

Materials and methods: Data was collected using the Crimson Clinical Advantage software. The software identified 64 patients who underwent major small and large bowel surgical procedures from July 2018 to February 2019. Patients' demographics, comorbidities, and treatment details were collected. Two groups where analyzed, patients that received alvimopan 12mg twice daily for up to 15 doses or until patients discharged, which ever occur first, with controls (patients who did not receive alvimopan). The data was retrospectively collected from patient records at Hialeah Hospital. The primary endpoints included reduction in both length of stay and total direct cost.

Results: The study reviewed 64 patients that met the inclusion criteria, 33 (51.5%) of these patients received alvimopan. When comparing both groups, alvimopan treatment was associated with a reduced duration mean of hospitalization (4.48 vs 7.39 days, $P < 0.01$). In addition, almivopan was also associated with a significant reduction of the average total direct cost for treatment group ($7,965 vs $9,100), a difference of 12.4%.

Conclusion: Patients who undergo segmental bowel resection with primary anastomosis and received alvimopan had a reduction of the length of stay and total direct costs compared with control group.

INTRODUCTION

Postoperative ileus (POI) may be defined as the impairment of gastrointestinal (GI) motility after intra-abdominal or nonabdominal surgery. It is characterized by bowel distention, lack of bowel sounds, accumulation of GI gas and fluid, and delayed passage of flatus and stool[1]

Postoperative ileus may result from the use of postsurgical opioid pain relievers, which can slow or inhibit normal motility[2]. Opioid analgesics relieve pain by blocking pain signals through stimulation of opioid receptors (mu receptors) located on the surface of the nerves that transmit these signals. Opioid analgesics bind to the mu receptors in the central nervous system (CNS) and the GI tract. The binding of opioid analgesics to mu receptors in the GI tract decrease intestinal motility, consequently disrupting normal GI function. The slowing of intestinal motility may cause significant discomfort and pain. Increased doses of opioid analgesics are related to extended periods of POI.

Major small and large-bowel procedures is an umbrella term for a variety of different complicated abdominopelvic surgical procedures. Typically, these procedures are resections, excisions, bypasses, repairs, and drainage of any components of the bowels. The current retrospective study reviews patients that have undergone any abdominopelvic surgical conducted by the same surgeon. The major small and large-bowel procedure analyzed are shown in table 1.

Table 1: Surgical procedures analyzed
Resection of the large or small bowel
Repair Abdominal Wall
Bypass Transverse Colon to Cutaneous
Bypass Sigmoid Colon to Cutaneous
Excision of Right Large Intestine
Supplement Duodenum with Autol Substitution
Drainage of Rectum
Excision of Small Intestine
Excision of Rectum

In these patients' populations, opioids are considered the standard of care for perioperative and postoperative pain management; however, they bind to mu-opioid receptors in the gastrointestinal tract and as result increase the risk of delayed recovery of the GI tract and postoperative ileus. Delayed gastrointestinal recovery after bowel resection increases the risk of in-hospital morbidity, and it is the most common cause of prolonged length of stay.

Entereg (alvimopan) is an oral peripheral acting μ-opioid receptor antagonist that help reduce opioids postoperative gastrointestinal side effect without reducing the pain-relieving effects.

Alvimopan was approved by the Food and Drug Administration (FDA) in May 2008 as a treatment to accelerate gastrointestinal recovery following partial large or small bowel resection with primary anastomosis[4]. It selectively and competitively binds to the GI tract mu opioid receptors and antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion. It does not affect opioid analgesic effects or induce opioid withdrawal symptom. The recommended adult dosage of alvimopan is 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery until discharge for a maximum of 7 days[4].

An advantage of alvimopan treatment is reduced hospital length of stay after bowel resection surgery with primary anastomosis and faster GI recovery[5]. There was a greater incidence of myocardial infarction (MI) in alvimopan-treated patients compared to placebo-treated patients in a 12-month clinical trial, although a causal relationship has not been established. Because of the potential risk of MI with long-term use, alvimopan is available only through a restricted program for short-term use (≤15 doses) under a Risk Evaluation and Mitigation Strategy (REMS) called the Alvimopan REMS Program. Alvimopan is restricted for in-hospital use only and only hospitals that have registered through the ENTEREG Access Support and Education (E.A.S.E. ™) Program and meet all requirements may use.

Hialeah Hospital has an alvimopan pre-operative and post-operative protocol that physicians must

fill prior dispensing to make sure patient meet criteria[6-7]. Refer to table 2 for alvimopan dosing.

Table 2: Dosing and administration
The recommended adult dosage of ENTEREG is: • 12 mg administered 30 minutes to 5 hours prior to surgery • Followed by 12 mg twice daily beginning the day after surgery • For a maximum of 7 days or until discharge
Patients should not receive more than 15 doses of ENTEREG.

Hialeah Hospital conducted a study to evaluate the cost-benefit of patients who underwent partial large or small bowel resection that received alvimopan versus patients who did not receive alvimopan treatment

METHODS

Study Design

We conducted a retrospective review for patients who underwent major small or large bowel surgical procedure with primary anastomosis at Hialeah Hospital by a single surgeon to compare costs and length of stay between patients receiving alvimopan and controls. All interventions were made prior to the commencement of the study.

Study population

The study population included any adult patient above the age of 18, with a range between 26-93 years old. During the time between July 2018 through February 2019, 64 patients underwent a major small or large bowel surgical procedure with primary anastomosis at Hialeah Hospital by a single surgeon. Two groups of patients were reviewed, patients who received alvimopan and patients who did not receive the treatment (control group). Patients with diagnosis-related group (DRG) codes 329, 330, 331, and 346 met the inclusion criteria. DRG 329 is defined as major small-bowel and large-bowel procedures with major comorbidities, DRG 330 is defined as major small-bowel and large-bowel procedures with comorbidities (not major comorbidities), DRG 331 is defined as major small-bowel and large-bowel procedures without any comorbidities and DRG 346 is defined as minor small & large bowel procedures without any comorbidities. Hence, the DRG codes used can be classified as 329 (the most complicated cases), 330 (intermediate), and 331 (the least complicated). Patient charts were retrospectively reviewed at minimum 30 days after patient discharge. The patient inclusion and exclusion criteria are found in table 3 and 4.

Table 3: Inclusion criteria for alvimopan (Entereg®)
Patient will be undergoing a partial large or small bowel resection
The patient has not taken therapeutic doses of an opioid for more than 7 consecutive days prior to surgery
The patient does not have a bowel obstruction.
The patient does not have severe hepatic dysfunction (Child-Pugh class C) or end-stage renal dysfunction
The patient can take oral medications. Alvimopan (Entereg®) is a hard gelatin matrix tablet and CANNOT be given via any tube (NG, OG, PEG, etc.) or crushed

Table 4: Exclusion criteria
Patients who did not meet the pre-operative and post-operative criteria to take alvimopan
Patients that underwent any GI surgery with a different surgeon
Patients under the age of 18

Data were collected from Crimson Clinical Advantage software, a software used to keep complete patient hospitalization records. The data points collected included: Patient's Financial Identification Number (FIN), patient age, patient gender, MS-DRG (Medicare-severity diagnosis-

related group (MS-DRG), Diagnosis Related Groups (APR-DRG), severity level, mortality risk, admit Date, discharge date, procedure date, LOS, primary Surgeon, number of Entereg® doses, direct variable supply costs, and procedure description.

Study endpoints

The first primary endpoint measured was the length of stay in the hospital. This outcome is defined as the number of days from the date of surgery to the date when patient was discharged. The second primary endpoint was the total direct health care costs difference between alvimopan treated patients and control group. The health care cost of each admission included medical supplies, labor, and equipment.

Post-surgical care

Standard postoperative care was provided to all patients included in the study, with or without alvimopan use. The post-operative protocol is found in table 5.

Table 5: Post-operative protocol
IV Opioid administration with rate adjustment based on age and side effects. Opioids are given as needed (Morphine, Hydromorphone)
Transition to Oral Opioids generally on post-operative day 1-4, with the goal to wean down before discharge. However, some patients had to be kept on IV opioids for an extended time
Patients were kept nothing-by-mouth (NPO) for 1-3 days, or until bowel function normalizes
Antibiotic prophylaxis for ≤ 24 hours
Monitoring vital signs and patient's recovery of bowel function

Description of the Intervention

Alvimopan was administered 12 mg 30 minutes prior surgery, then 12 mg orally twice daily beginning the day after the surgery for up to 15 doses or until hospital discharged, whichever occurred first.

Statistical analysis

A z-test and t-test were conducted using Microsoft excel to calculate if there is a significant difference between the average LOS between both patient groups.

RESULTS

We included 64 patients who underwent small-bowel or large-bowel resection during the study period performed by same surgeon. For all patients, surgeon followed Hialeah Hospital Alvimopan (Entereg®) pre-operative and post-operative protocol prior dispensing.

The P-value for the difference in means of LOS in both patient groups was calculated. It was concluded that alvimopan was able to reduce the mean LOS by 2.91 days, P-value of 0.017.

z-Test: Two Sample for Means

	Variable 1	*Variable 2*
Mean	7.387096774	4.484848485
Known Variance	29.645	14.257
Observations	31	33
Hypothesized Mean Difference	0	
z	2.463143284	
P(Z<=z) one-tail	0.006886243	
z Critical one-tail	1.644853627	
P(Z<=z) two-tail	0.013772486	
z Critical two-tail	1.959963985	

t-Test: Two-Sample Assuming Unequal Variances

	LOS w/o alvimopan	*LOS with alvimopan*
Mean	7.387096774	4.484848485
Variance	29.64516129	14.25757576
Observations	31	33
Hypothesized Mean Difference	0	
df	53	
t Stat	2.463123191	
P(T<=t) one-tail	0.00852752	
t Critical one-tail	1.674116237	
P(T<=t) two-tail	0.017055041	
t Critical two-tail	2.005745995	

Table 6 Descriptive Clinical Characteristics by Drug Status

Variable	**Without Alvimopan (n=31)**	**With Alvimopan (n=33)**
DRG [(n (%)]		
- 329	4 (12.9)	0
- 330	15 (48.3)	17 (51.5)
- 331	10 (32.3)	15 (45.5)
- 346	2 (6.4)	1 (3)
Sex		
- Female	18	20
- Male	13	13
Age (years) [mean (SD)]	66.68(14.3)	73.2 (12.6)
Intestinal cancer [n, (%)]	10 (32.2)	13 (39.4)
Diverticular disease [n, (%)]	5 (16.1)	5 (15)
Benign Neoplasm [n, (%)]	4 (12.9)	10 (30.3)
Total Severity Level [mean]	2	1.7
- Minor [n, (%)]	9 (29)	12 (36.4)
- Moderate [n, (%)]	14 (45.1)	17 (51.1)
- Major [n, (%)]	5 (16.1)	4 (12.1)
- Extreme [n, (%)]	4 (12.9)	0

DRG = Diagnosis-Related Group; SD = standard deviation.
DRG codes refer to major small-bowel and large-bowel procedures. Code 329 includes major comorbid conditions, Code 330 refers to other comorbid conditions, and Code 331 refers to no comorbid conditions
Severity level= minor=1, moderate=2, major=3 and extreme=4

Table 7 Primary Outcome Variable by Drug Status		
Variable	**Without Alvimopan (n=31)**	**With Alvimopan (n=33)**
Total LOS days [mean SD]	7.39 (6.05)	4.48 (3.77)
LOS by DRG [mean] days		
- 329	16.25	--
- 330	7.73	5.41
- 331	5.01	3.40
- 346	5.50	5.0
Direct Variable Supply Costs [mean]	$ 3,794	$ 4,312
Direct Costs [mean]	$9,100	$ 7, 965
30 Days Readmissions (n, %)	5 (16.67)	2 (6.06)

LOS = length of stay DRG = Diagnosis-Related Group; SD = standard deviation.
DRG codes refer to major small-bowel and large-bowel procedures. Code 329 includes major comorbid conditions, Code 330 refers to other comorbid conditions, and Code 331 refers to no comorbid conditions.
Direct Variable Supply= Variable costs pertaining to patient supplies, and that increase/decrease with the patient load and case volume. These do not include any fixed or indirect costs.
Direct Costs= Costs attributable to specific sources, such as department costs. These costs do not include indirect, or overhead costs that are common to everybody (such as electricity and administrative staff).

Table 6 lists the patients' clinical characteristics according to treatment. The rate of drug utilization in the 329 DRG class was 0 %. The corresponding rate of drug use for class 330 DRG patients was 53.1%, the rate for class 331 DRG was 60% and the rate of DRG 346 was 33% . Thus, there was a significant increase in drug utilization as the DRG class became less severe.

Patient receiving alvimopan had less severity of post-operative complications compared with control (2 vs. 1.7). Patients treated with alvimopan had a total LOS equal to 4.48 days vs. 7.39 the control group, with a mean difference of 2.91 days. Direct variable supply costs, which included medication cost represented $4,312 with alvimopan treated vs. $3,794 in the control. This was due to the cost of alvimopan which is $165 per tablet. However, the total direct cost was more in the control vs alvimopan treated patients ($9,100 vs. $7,965). Thirty-day readmission rate was significantly less in alvimopan-treated patient representing 6.06 % versus 16.67% in non-alvimopan treated patient.

DISCUSSION

Total hospital costs were $1,135 less for alvimopan treated patients than for control group who did not receive alvimopan. In addition, mean hospital length of stay was shorter by almost 3 days for alvimopan patients than for matched controls. Thirty-day readmission rate was significantly less in alvimopan-treated patient representing 6.06 % versus 16.67% in non-alvimopan treated patient

Delayed GI recovery or POI after abdominal surgery costs the American health care system approximately $1.46 billion annually[8]

Previous clinical trials have demonstrated the ability of alvimopan to accelerate GI recovery[9-12] and decrease the incidence POI risk[13]. Alvimopan, therefore, can be expected to decrease the LOS and hospital costs associated with delayed GI recovery as concluded in other studies [3,8,14].
The length of stay of patients receiving alvimopan in this study was comparable to other related studies [3]. This study determined that there is a significant benefit of adding alvimopan to patients undergoing partial large or small bowel resection with primary anastomosis reduce total direct cost by reducing the LOS.

This study represent a great value because we were able to confirm data from actual work practice while clinical trials have a rigorous setting

Length of stay is an appropriate surrogate marker for the 30-day readmission rate [15]. The direct relationship between length of stay and 30-day readmission is still unclear and merits further studies to understand their relationship. However, it is known that the overall health of a patient also

influences LOS and 30-day readmission, respectively [16].

This study was a retrospective design, with a possibility for bias. To reduce selection bias patient data such as DRG codes was gathered to assess factors that can influence the measured outcomes. The data demonstrated that in both test groups, with DRG code 346, the LOS was comparable. Furthermore, records revealed variations of concomitant opioid use between both groups, which may be a possible confounding factor. Moreover, aside from all patients who underwent surgical procedure by the same surgeon and receive the same post-operative protocol, the potential of variations in care cannot be eliminated. These variations can result from drug administration technique, nursing practices, hospital capacity, and other possible changes over the hospitalization.

CONCLUSION

Our study confirmed that patients who received alvimopan after bowel surgery had significantly less hospital LOS compared with patient who did not received this drug. Alvimopan reduced the direct cost by an average of $1,135 based on this analysis.

Alvimopan represents a viable option for use in the perioperative management of patients undergoing segmental bowel resection with primary anastomosis

CONFLICT OF INTEREST

This study did not receive funding from any institution.

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