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# Multi-institutional outcomes and cost effectiveness of using alvimopan to lower gastrointestinal morbidity after cystectomy and urinary diversion

Anup Vora, MD, Daniel Marchalik, MD, Hanaa Nissim, MD, Keith Kowalczyk, MD, Gaurav Bandi, MD, Kevin McGeagh, MD, John Lynch, MD, Krishnan Venkatesan, MD, Reza Ghasemian, MD, Jonathan Hwang, MD, Mohan Verghese, MD

Departments of Urology, Georgetown University Hospital and Washington Hospital Center, Washington, DC USA

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**Introduction:** Radical cystectomy is associated with significant morbidity and cost, with rates of gastrointestinal complications as high as 30%. Alvimopan is a mu opioid receptor antagonist that has been shown in randomized-control trials to accelerate gastrointestinal recovery in patients undergoing bowel resection with primary anastomosis. We report our experience with gastrointestinal recovery for patients undergoing cystectomy with urinary diversion treated with alvimopan and cost benefit associated.

**Materials and methods:** Between January 2008 and October 2012, 80 patients underwent radical cystectomy with urinary diversion at two institutions. Forty-two patients in our study did not receive alvimopan preoperatively. Thirty-eight patients received perioperative alvimopan and were without postoperative nasogastric decompression. Return of bowel function, initiation of diet, and gastrointestinal complications and estimated cost of hospitalization were evaluated.

**Results:** Times to first flatus (3.1 days versus 4.7 days,  $p < 0.01$ , 95% CI 0.96-2.24) and bowel movement (3.9 days versus 4.9 days,  $p < 0.01$ , 95% CI 0.45-1.55) were significantly shorter in those patients who received alvimopan. Additionally, the initiation of clear liquid diet (4.1 days versus 5.5 days,  $p < 0.01$ , 95% CI 0.70-2.10), regular diet (5.2 days versus 6.3 days,  $p < 0.01$ , 95% CI 0.39-1.81) and hospital discharge (6.1 days versus 7.7 days,  $p = 0.04$ , 95% CI 0.01-3.21) were accelerated in the alvimopan cohort. There were no incidences of prolonged ileus in patients who received perioperative alvimopan (0% versus 26.2%,  $p < 0.01$ ).

With an approximate average cost of alvimopan administration \$825 per hospitalization, the average cost benefit of administration over control was \$1515 per hospitalization. The cost benefit was mainly a result of a shorter inpatient hospitalization and lack of gastrointestinal morbidity which accumulated a majority of the difference.

**Conclusion:** In our experience, the use of alvimopan perioperatively significantly accelerates the rate of gastrointestinal recovery and hospital discharge, eliminates the need for nasogastric tube decompression, and reduces the incidence of post-operative ileus in patients following radical cystectomy and urinary diversion.

**Key Words:** cystectomy, ileus, alvimopan, morbidity, complications

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Address correspondence to Dr. Anup A. Vora, Department of Urology, Washington Hospital Center/Georgetown University, 3B-19, 110 Irving St NW, Washington DC 20010 USA

## Introduction

Radical cystectomy, while being the gold standard treatment for muscle-invasive bladder cancer, is

associated with significant morbidity and mortality. Gastrointestinal complications are the most common cause of postoperative morbidity and lead to extended length of hospitalization. They account for significant clinical and economic burden with a reported annual hospital cost of \$1.46 billion.<sup>1</sup> Although overall complication rates with this surgery have decreased over the past 20 years, the rates of gastrointestinal complications remain as high as 30%.<sup>2-4</sup>

Numerous prospective trials, in both general surgery and urologic literature, have shown benefits from decreased nasogastric decompression and the utilization of accelerated postoperative pathways.<sup>1</sup> However, even with these interventions, rates of gastrointestinal morbidity are reported as high as 25%.<sup>5-9</sup> This can be largely attributable to opioids, the current standard for postoperative pain management, which bind to mu opioid receptors of the gut and delay recovery of the gastrointestinal tract. Opioid receptors (mu, delta, kappa) are present in both the central and the enteric nervous system, and its effect to slow intestinal transit comes from stimulation in the myenteric and submucosal bowel plexus.<sup>10,11</sup>

Over the past decade, extensive research has been performed to identify an agent to inhibit the gastrointestinal effect of opioids while not affecting analgesia, leading to the development of alvimopan.<sup>12,13</sup> Several randomized control trials in general surgery have shown that alvimopan accelerates gastrointestinal recovery in patients undergoing bowel resection with primary anastomosis.<sup>14-16</sup>

While we have first reported the use of alvimopan in a cohort of radical cystectomy patients,<sup>17</sup> challenges to the adoption of this medication remain. In our current medical climate, efficiency and cost accountability are of utmost importance to the delivery of patient care. We examine in this study the outcomes and cost benefit of using alvimopan in patients undergoing radical cystectomy and urinary diversion across multiple institutions.

## Materials and methods

Between January 2008 and October 2012, 80 consecutive patients underwent radical cystectomy with urinary diversion across two institutions (Georgetown University Hospital n = 20 and Washington Hospital Center n = 60, Washington DC, USA). Our first 23 patients underwent open cystectomy and did not receive alvimopan. Our hospital system then approved the use of alvimopan and the next 27 patients underwent open cystectomy and received alvimopan. Our hospital system then began performing robotic

cystectomy with proficiency and the next 30 patients underwent robotic cystectomy with alternation of administration of alvimopan. Sixty-three patients received neoadjuvant chemotherapy. All patients were seen by a multidisciplinary team composed of urology, medical and radiation oncology, stoma and palliative care services. Patients were counselled on both continent and conduit urinary diversions regarding quality-of-life, technical feasibility, and potential oncologic outcomes with the ultimate decision based on patient wishes.

### *Preoperative care*

All patients received a clear liquid diet and a mechanical bowel prep with polyethylene glycol (Go-Lytely, Braintree, MA, USA) the day before surgery. Forty-two patients in our study did not receive alvimopan preoperatively, while 38 patients received their first dose of alvimopan (12 mg PO) at least 1 hour prior to the induction of anesthesia. Patients were excluded from our study if they had received opioids within 1 week of surgery or had a previous history of multiple bowel resections.

### *Surgical procedure*

Following induction of anesthesia, all patients received nasogastric tube decompression. Standard radical cystectomy and bilateral pelvic lymphadenectomy was performed. Thirty patients underwent robotic assisted radical cystectomy. Terminal ileum was used in all patients for both continent and non-continent diversions. After isolating the chosen segment of ileum, bowel continuity was restored using gastrointestinal stapling devices.

### *Postoperative management*

In patients who received alvimopan, the nasogastric tube was removed at time of extubation. They were then started on postoperative alvimopan dosing of 12 mg PO bid until the initiation of a diet or a maximum of 15 doses was achieved. Patients who did not receive alvimopan had selective removal of their nasogastric tube based on bowel sounds, flatus and clinical status. Opioid patient-controlled anesthesia pumps or an epidural infusion with fentanyl was used for postoperative pain management. Transition to oral opioids was performed after successful initiation of diet.

Clear liquid diet was initiated after first flatus and was advanced to a regular diet typically within 24 hours after toleration of clear liquids (no nausea or emesis). A nasogastric tube was reinserted in patients with prolonged ileus or bowel obstruction, and total parenteral nutrition was initiated on postoperative

day 7 if bowel complications persisted. Postoperative ileus was defined as the persistent absence of flatus and bowel movement on postoperative day 7 with associated radiographic findings on abdominal x-ray.

### Statistical analysis

Data was collected retrospectively into an institutional review board approved database. Preoperative variables, including age, gender, body mass index, were compared between the two groups. Return of bowel function, advancement of diet, length of nasogastric decompression, duration of hospital stay, and gastrointestinal complications were used as study endpoints. Estimated cost of hospitalization was based on all hospital charges including operating room and post-operative care expenses. Costs were assessed by determining the net cost of alvimopan use and subsequent reduction in length of stay. All statistical analyses were performed using SPSS statistical software (IBM, Armonk, NY, USA) and groups were compared using a two-tailed paired t-test and a multivariate analysis of variation.

### Results

The two groups had comparable preoperative demographics (age, sex, smoking status and body mass index) and comorbidities with no variable of statistical significance on multivariate analysis, Table 1. In the group receiving alvimopan, times to first flatus (3.1

days versus 4.2 days,  $p < 0.01$ , 95% CI 1.89-2.82) and bowel movement (3.8 days versus 5.0 days,  $p < 0.01$ , 95% CI 1.93-2.36) were significantly shorter than those who did not receive it. Additionally, the initiation of clear liquid diet (4.2 days versus 5.3 days,  $p < 0.01$ , 95% CI 1.76-3.01), regular diet (4.9 days versus 5.9 days,  $p = 0.03$ , 95% CI 0.32-2.18) and hospital discharge (6.1 days versus 7.7 days,  $p = 0.04$ , 95% CI 0.03-3.89) were accelerated in the alvimopan cohort. Patients who were not given alvimopan were maintained with nasogastric tube decompression for a mean of 4.1 days while those who received it were without a nasogastric tube for their entire postoperative course, Table 2.

There were no incidences of prolonged ileus and no requirements for total parenteral nutrition in patients pretreated with alvimopan. However, one quarter of the patients in the group not receiving alvimopan required nasogastric tube decompression and initiation of parenteral nutrition for prolonged ileus (0% versus 26.1%,  $p = 0.015$ ). The rate of non-gastrointestinal complication (28.9% versus 30.9%,  $p = 0.84$ ) was also not statistically significant between the two groups, Table 3.

With an approximate average cost of alvimopan administration \$625 per hospitalization (10.2 mean doses), the average cost benefit of administration over control was \$1515 per hospitalization. The cost benefit was mainly a result of a shorter inpatient hospitalization and lack of gastrointestinal morbidity which accumulated a majority of the difference.

TABLE 1. Perioperative patient demographics

	Alvimopan (n = 38)	Control (n = 42)	p value
Age	67.9	68.8	0.65
% male	63.2 (24/38)	73.8 (31/42)	0.31
% smoking history	78.9 (30/38)	81.0 (34/42)	0.83
Body mass index	24.4	29.7	0.88
% hypertension	73.6 (28/38)	73.8 (31/42)	0.78
% diabetes mellitus	47.3 (18/38)	42.8 (18/42)	0.82
% coronary artery disease	36.8 (14/38)	33.3 (14/42)	0.56
% hyperlipidemia	63.1 (24/38)	52.3 (22/42)	0.48
% gastroesophageal reflux disease	26.3 (10/38)	19.0 (8/42)	0.52
% ethanol abuse	07.8 (3/38)	0.0 (0/42)	0.10
% atrial fibrillation	05.2 (2/38)	0.02 (1/42)	0.21
% neoadjuvant chemotherapy	78.9 (30/38)	78.6 (33/42)	0.89
% robotic-assisted	39.4 (15/38)	35.7 (15/42)	0.46

TABLE 2. Perioperative patient outcomes. All lengths are in days

	Alvimopan	Control	p value
Estimated blood loss (cc)	507.5	509.4	0.95
Operative time (min)	326.1	325.9	0.98
% epidural PCA	31.6 (12/38)	33.3 (14/42)	0.86
% ileal conduit urinary diversion	73.7 (28/38)	78.5 (33/42)	0.61
% ileal neobladder	26.3 (10/38)	21.5 (9/42)	0.61
Duration of NGT (days)	0	4.1	< 0.01
Time to flatus (days)	3.11	4.24	< 0.01
Time to first bowel movement (days)	3.81	4.98	< 0.01
Initiation of sips (days)	3.21	4.34	< 0.01
Initiation of clear liquids (days)	4.18	5.32	< 0.01
Initiation of regular diet (days)	4.91	5.89	0.03
Length of hospital stay (days)	6.08	7.74	0.04
% Requiring TPN	0	26.1 (11/42)	0.015

PCA = patient controlled analgesia; NGT = nasogastric tube; TPN = total parenteral nutrition

## Discussion

Radical cystectomy and urinary diversion are associated with serious postoperative complications with the 90 day morbidity rate reported as high as 64%. The majority of these complications usually develop early, and gastrointestinal complications are the most frequent in the postoperative period.<sup>3</sup> The etiology of prolonged ileus after bowel reconstruction is multifactorial, and while it is inevitable that some degree of ileus will accompany any bowel resection, the duration is often exacerbated by intraoperative and postoperative narcotics used for induction and pain control.

Other agents such as metoclopramide,<sup>18</sup> erythromycin,<sup>19-20</sup> neostigmine,<sup>21</sup> propranolol<sup>22</sup> and chewing gum<sup>23</sup> have also been extensively researched in the past to improve gastrointestinal outcomes after bowel reconstruction, but no single agent has shown consistent benefits. Multimodal perioperative algorithms for patients undergoing cystectomy have also been investigated with the goal of improving the rate of gastrointestinal recovery. Strategies have included the use of non-opioid analgesia, early ambulation and early nasogastric tube removal.<sup>8,9</sup>

Alvimopan is a quaternary mu opioid receptor antagonist that inhibits enteric receptors while preserving central analgesia. Its chemical structure

TABLE 3. Perioperative complications (%)

	Alvimopan (n = 38)	Control (n = 42)	Clavien Grade <sup>30</sup>
Prolonged Ileus/SBO (requiring NGT insertion)	0	11 (26.1)	IIIa
Wound infection	6 (15.7)	8 (19.0)	II
Deep vein thrombosis	2 (5.26)	3 (7.14)	II
Acute alcohol withdrawal	1 (2.6)	0	II
Wound deshiscence	1 (2.6)	1 (2.4)	IIIb
Cardiac arrhythmia	1 (2.6)	1 (2.4)	II

SBO = small bowel obstruction; NGT = nasogastric tube



is similar to naloxone, a competitive antagonist of mu receptors and known opioid antidote, however, alvimopan does not penetrate the blood-brain barrier; thus preventing antagonism of the central receptor.<sup>12</sup> The drug was approved by the Federal Drug Administration (FDA) in 2008 for acceleration of gastrointestinal recovery after primary bowel resection. This approval was primarily based upon three North American randomized, double-blind, placebo-controlled, parallel-group, phase III trials and a single European phase III trial which have shown alvimopan to shorten gastrointestinal convalescence and decrease incidence of postoperative ileus after bowel resection.<sup>15,24</sup>

As we have previously defined its beneficial role in reducing the rate of gastrointestinal morbidity after radical cystectomy,<sup>17</sup> our follow up study questions whether giving alvimopan to all patients undergoing radical cystectomy is cost effective. In a post hoc analysis of the four North American randomized trials that led to FDA approval, Bell et al showed that the mean estimated hospital cost was \$897-\$977 less in the alvimopan group undergoing colorectal bowel resections.<sup>25</sup> Alvimopan was also cost saving for prevention of postoperative ileus in patients undergoing bowel resection by laparotomy, although these potential cost savings were highly dependent on a difference in time to discharge order written.<sup>26</sup> This finding was not applicable to the less-invasive laparoscopic surgical approach for which quality data on alvimopan use are lacking.

This is an important consideration for radical cystectomy patients as there is increasing utilization of robotic instruments to provide a minimally invasive approach.<sup>27</sup> As robotic cystectomy has been shown to trend toward a decreased rate of excessive length of stay (greater than 5 days)<sup>28</sup> this could likely affect the cost-benefit of using alvimopan in those patients. A recent study<sup>29</sup> evaluated alvimopan in radical cystectomy patients within a cost-effectiveness model. They concluded that the likelihood of postoperative ileus gave the most impact towards the cost benefit of alvimopan (an incidence of 14% was needed to achieve cost equivalence, while an incidence of 30% resulted in a cost advantage of \$837 per patient).<sup>29</sup>

Regarding nasogastric decompression, we feel that the absence of a postoperative nasogastric tube (alvimopan cohort) allows those patients to have a significant clinical advantage in terms of faster gastrointestinal recovery and overall comfort. While we acknowledge that in many centers post-operative nasogastric tubes are not utilized routinely after urinary diversion, this is not standard of care and

we still encourage its use in patient's not receiving alvimopan (control group) until flatus returns. The rate of nasogastric tube reinsertion in patients whom have it removed after surgery without alvimopan has been reported to be as high as 20%.<sup>5-7</sup> While this contrast between cohorts can be viewed as a selection bias, we highlight that in our study the reinsertion rate was 0% for patients receiving alvimopan and 26.1% in patients who did not and we conclude this difference is result of the protective benefit of alvimopan.

In our review, the use of alvimopan continued to significantly improved gastrointestinal convalescence in patients undergoing urinary diversion and radical cystectomy. The return of flatus and bowel movements ( $p < 0.001$ ) and time to hospital discharge were accelerated ( $p = 0.04$ ). As our incidence of gastrointestinal morbidity in our control approached 30%, we feel that the use of alvimopan provides cost-effective benefit based on published predictive cost-effective models.<sup>29</sup> Additionally, the total cost benefit per patient for our health systems was \$1515 which was largely attributable to decrease length of hospitalization.

Our study is not without its limitations. When compared to other studies in contemporary literature, our length of hospitalization are comparatively longer. We feel that socioeconomic factors (placement, home care, etc) of our urban population delayed hospital discharge for patients in both cohorts. We also recognize that our decision to include both robotic and open surgical patients may lead to a selection bias. We included both types as we feel that it accurately represents current operative trends in urology. Additionally, proponents of robotic surgery may feel the minimally invasive approach will preclude any benefit of alvimopan and our study proves there remains a benefit even within robotic surgery. We included the same number of robotic patients in both groups and feel there is no significant selection bias. Despite these limitations, we believe our study is of clinical significance to urologists who encounter and manage patients post urinary diversion with regard to gastrointestinal morbidity.

## Conclusion

Urinary diversion status post radical cystectomy is associated with significant gastrointestinal morbidity. Our continued experience with alvimopan in patients undergoing radical cystectomy and urinary diversion demonstrates accelerated rates of gastrointestinal recovery and hospital discharge, reduced incidence of postoperative ileus and reduced total cost of hospitalization. □

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