A comparison of naloxegol versus alvimopan at the time of cystectomy and urinary diversion

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Introduction: *The use of alvimopan at the time of cystectomy has been associated with improved perioperative outcomes. Naloxegol is a less costly alternative that has been used in some centers. This study aims to compare the perioperative outcomes of patients undergoing cystectomy with urinary diversion who receive the mu-opioid antagonist alvimopan versus naloxegol.*

Materials and methods: *This was a retrospective review that included all patients who underwent cystectomy with urinary diversion at our institution between 2007-2020. Comparisons were made between patients who received perioperative alvimopan, naloxegol and no mu-opioid antagonist (controls).*

Results: *In 715 patients who underwent cystectomy, 335 received a perioperative mu-opioid antagonist, of whom 57 received naloxegol. Control patients, compared to naloxegol and alvimopan patients, experienced a significantly ($p < 0.05$) delayed return of bowel function (4.3 vs. 2.5 vs. 3.0 days) and longer hospital length of stay (7.9 vs. 7.5 vs. 6.5 days), respectively. The incidence of nasogastric tube use (14.2% vs. 12.5% vs. 6.5%) and postoperative ileus (21.6% vs. 21.1% vs. 13.3%) was also most common in the control group compared to the naloxegol and alvimopan cohorts, respectively. A multivariable analysis revealed that when comparing naloxegol and alvimopan, there was no difference in return of bowel function (OR 0.88, $p = 0.17$), incidence of postoperative ileus (OR 1.60, $p = 0.44$), or hospital readmission (OR 1.22, $p = 0.63$).*

Conclusions: *Naloxegol expedites the return of bowel function to the same degree as alvimopan in cystectomy patients. Given the lower cost of naloxegol, this agent may be a preferable alternative to alvimopan.*

Key Words: cystectomy, postoperative ileus, small bowel obstruction

Introduction

Cystectomy with urinary diversion is a major surgery associated with significant morbidity. The most frequent complications typically involve the gastrointestinal tract and include issues such as postoperative ileus and/or small bowel obstruction.[1,2] Advances in the perioperative management in patients undergoing cystectomy have been associated with improved perioperative outcomes and reduction in the frequency of these gastrointestinal complications. Such examples include enhanced recovery after surgery (ERAS) protocols, which involve early ambulation, early feeding, limiting narcotic use, increased use of regional anesthetic blocks, and use of mu-opioid antagonists at the time of surgery.[3,4]

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Alvimopan is a mu-opioid antagonist that has previously demonstrated efficacy in accelerating gastrointestinal recovery and shortening hospital length of stay (LOS) in a randomized double-blind placebo-controlled trial in patients undergoing radical cystectomy.[5,6] Since this study, its use has increased in the United States in centers performing cystectomy.[7] Another member of the mu-opioid antagonist family, naloxegol, had previously been investigated as a potential cost-effective alternative to alvimopan in a single-center respective series and demonstrated similar efficacy when assessing hospital LOS and development of postoperative ileus (POI).[8] As a result, we implemented naloxegol in our perioperative cystectomy protocol in 2018. However, there is scant data regarding how these agents compare with respect to objective measures of gastrointestinal function after cystectomy, including time until return of bowel function.

In this context, we reviewed our experience with both agents at our institution and aimed to compare gastrointestinal function in patients undergoing cystectomy who received either agent. This study provides additional insight into the comparative efficacy of these drugs and whether one demonstrates superior outcomes in the perioperative setting of patients who undergo cystectomy.

Materials and methods

Data source

This is a retrospective study that included all patients who underwent cystectomy with urinary diversion at our institution between 01/01/2007-06/01/2020.

Patient selection

After institutional board review, we queried the electronic health records for adult patients who underwent cystectomy with urinary diversion for any indication.

Variables

Data were collected for the following patient characteristics: demographics (age, BMI, sex), insurance status, smoking and alcohol status, comorbidities (Charlson Comorbidity index-CCI), Eastern Cooperative Oncology Group (ECOG) status, operative indication, prior abdominal surgeries, history of abdominal radiation therapy. Data was also collected on whether patients chronically used opioids.

Alvimopan was introduced into our treatment pathway for cystectomy patients in 2013. This medication was administered to all patients undergoing cystectomy for any indication before surgery as a single dose, followed by twice per day dosing until the patient had return of bowel function. Once bowel function returned, the medication was discontinued. Naloxegol was introduced into our practice in 2018 as an alternative to alvimopan mainly due to its cost-effective nature and some evidence suggesting similar effect as alvimopan in the perioperative setting. Patients excluded from mu-opioid antagonist use included patients who used chronic opioids and those with significant cardiac events within the prior year of surgery.

Data regarding perioperative outcomes such as hospital LOS, days until return of bowel function, ability to tolerate clear liquid diet, and ability to tolerate solid diet, postoperative ileus/small bowel obstruction, need for nasogastric tube placement, postoperative complications, and incidence of hospital readmission, were collected. Return of bowel function was defined as the presence of flatus documented in the hospital notes. Postoperative ileus was noted when one of more of the following were present: radiographic description of intestinal distention consistent with ileus, need for nasogastric tube decompression after surgery, delayed bowel function return of more than 6 days after surgery.

Statistical analysis

Continuous variables were summarized with mean (SD) or median (IQR), while categorical variables were summarized with count (percentage). Univariate analysis was done using Pearson Chi-squared test or Fisher exact test. Continuous variables were evaluated with a Kruskal-Wallis test. Univariate analysis was performed to assess the association between covariates with outcomes of interest. A multivariable logistic regression analysis was performed to model the probability of postoperative ileus and readmission. A Poisson regression analysis was performed to model time until return of bowel function and hospital LOS. Covariates for the multivariable models were selected on an a priori basis, as well as variables significantly associated with outcomes of interest on univariate analysis. The association between the covariates and the outcomes were quantified by odds ratio. The point estimates and the 95% confidence interval (CI) were reported. Statistical analyses were conducted using R 4.0.3 (R Project for Statistical Computing), and p values $< .05$ were considered significant.

Results

In 715 patients who underwent cystectomy, 408 patients underwent surgery since implementation of alvimopan in our perioperative protocol. In these 408 patients, 335 (82.1%) received a perioperative

mu-opioid antagonist. Fifty-seven patients (17.0%) received naloxegol, while the remaining 278 (83%) received alvimopan. There was no difference between the cohorts with respect to baseline characteristics, Table 1, with the exception of age-adjusted CCI, where there was a higher age-adjusted CCI in the naloxegol cohort. The robotic approach was more common in patients who received naloxegol vs. alvimopan (66.7% vs. 39.2%, respectively, $p < 0.001$).

On initial analysis we compared control patients (no mu-opioid antagonist) to patients who received naloxegol or alvimopan. Control patients, compared to naloxegol and alvimopan patients, experienced a significantly ($p < 0.05$) delayed return of bowel function (4.3 vs. 2.5 vs. 3.0 days), longer hospital LOS (7.9 vs. 7.5 vs. 6.5 days), delayed time until tolerating liquid diet (5.0 vs. 1.5 vs. 3.5 days) and delayed time until tolerating a regular diet (6.3 vs. 4.9 vs. 4.7 days), respectively. The incidence of nasogastric tube use and postoperative ileus was also most common in the control group (14.2% and 21.6%, respectively).

A univariate and multivariable analysis were also done that analyzed all three groups and on multivariable analysis, both alvimopan and naloxegol were associated with quicker return of bowel function, (alvimopan OR 0.68, naloxegol OR 0.66) compared to control patients. However, only alvimopan was associated with reduced hospital LOS (OR 0.80) and reduced odds of developing a postoperative ileus (OR 0.52), compared with control patients.

When comparing objective measures of return of bowel function between the two mu opoid antagonists, Table 2, the naloxegol cohort experienced a quicker median return of bowel function (2.0 vs. 3.0 days, respectively, $p = 0.01$), and quicker time to liquid (1.0 vs. 3 days, $p < 0.001$) and regular diet (3.5 vs. 4 days,

TABLE 1. **Patients characteristics of alvimopan versus naloxegol cohorts**

	Alvimopan (n = 278)	**Naloxegol (n = 57)**	**p value**
Age, median (IQR)	72.0 (65.0-77.0)	73.0 (65.0-77.0)	0.71
Sex			0.26
Male	209 (75.5)	47 (82.5)	
Female	68 (24.5)	10 (17.5)	
BMI, median (IQR)	27.7 (24.2-31.3)	26.9 (24.1-30.1)	0.23
Race			0.61
White	263 (94.6)	52 (92.9)	
Other	15 (5.4)	4 (7.1)	
CCI, median (IQR)	4.0 (3.0-5.0)	5.0 (3.5-6.0)	< 0.001
Ecog status			0.09
Grade 1	123 (44.7)	33 (58.9)	
Grade 2	122 (44.4)	16 (28.6)	
Grade 3-5	30 (10.9)	7 (12.5)	
History of diabetes mellitus	36 (12.9)	6 (10.5)	0.62
Prior abdominal surgical history	178 (64.3)	36 (64.3)	> 0.99
Prior abdominal radiation therapy	33 (12.2)	3 (13.6)	0.84
Clinical stage			
Tis	17 (6.1)	2 (3.5)	0.162
Ta	12 (4.3)	1 (1.8)	
T1	57 (20.5)	18 (31.6)	
T2	122 (43.9)	27 (47.4)	
T3	19 (6.8)	1 (1.8)	
T4	6 (2.2)	1 (1.8)	
Non-malignant indication	40 (14.4)	4 (7.0)	
Non-bladder indication	5 (1.8)	3 (5.3)	

IQR = interquartile range; BMI = body mass index; CCI = Charlson Comorbidity Index

TABLE 2. **Perioperative outcomes of alvimopan versus naloxegol cohorts**

	Alvimopan (n = 278)	Naloxegol (n = 57)	p value
Surgical approach			< 0.001
Open	169 (60.8)	19 (33.3)	
Robotic	109 (39.2)	38 (66.7)	
Return of bowel function, median (IQR), days	3.0 (2.0-3.0)	2.0 (2.0- 3.0)	0.01
Hospital LOS, median (IQR), days	6.0 (5.0-7.0)	6.0 (5.0-7.0)	0.34
Time to liquid diet, median (IQR), days	3.0 (3.0-4.0)	1.0 (0.0-2.0)	< 0.001
Time to regular diet, median (IQR), days	4.0 (4.0-5.0)	3.5 (3.0-4.25)	0.001
Need for nasogastric tube			0.12
No	260 (93.5)	49 (87.5)	
Yes	18 (6.5)	7 (12.5)	
Complications			
Ileus/small bowel obstruction	37 (13.3)	12 (21.1)	0.13
Myocardial infarction	2 (0.7)	0 (0.0)	0.52
Urinary tract infection	24 (8.6)	12 (21.1)	0.006
Sepsis	19 (6.8)	7 (12.3)	0.16
ICU admission	20 (7.2)	6 (10.5)	0.39
Failure to thrive	17 (6.1)	1 (1.8)	0.18
Arrhythmia	16 (5.8)	4 (7.0)	0.71
Readmission	61 (21.9)	17 (29.8)	0.20

IQR = interquartile range; LOS = length of stay

p = 0.001). Cardiac complications were rare and did not differ between the cohorts. The incidence of other complications was also similar between the cohorts.

Univariate models were constructed to identify factors associated with return of bowel function, hospital LOS, development of postoperative ileus, and hospital readmission, Table 3. On multivariable analysis, Table 4, there was no difference between naloxegol and alvimopan when assessing return of bowel function (OR 0.86, p = 0.15), incidence of postoperative ileus (OR 1.60, p = 0.44), or hospital readmission (OR 1.22, p = 0.63). With hospital LOS, however, naloxegol was associated with increased hospital LOS on multivariable analysis (OR 1.37, p < 0.001).

Discussion

In this study, we observed a null association between choice of mu-opioid antagonist and objective measures of the return of bowel function after cystectomy. Secondly, we observed a null association between antagonist choice and postoperative ileus rates and readmission rates, though in the case of ileus, the raw differences were larger than expected and the null association may be an issue of power. Lastly, we observed that naloxegol may be associated with a longer LOS, but we suspect that this observation is at least in part related to variation in surgeon preferences regarding the expediency of discharge. Nevertheless, taken together, these findings form the basis for the preferential use of naloxegol over alvimopan since the former is drastically lower in price and the outcomes related to return of GI function are statistically similar.

Gastrointestinal complications at the time of cystectomy are the most frequent complications after surgery and include postoperative ileus and small bowel obstruction.[2] Most cases can be managed conservatively, but occasionally intervention is required. These complications are associated with prolonged hospital LOS and as a result, an increased cost-burden on the healthcare system. This is supported by a study by Mossanen et al, where authors analyzed 9,137 patients who underwent radical cystectomy from 360 hospitals from 2003-2013 and sought to characterize the association of postoperative complications with costs after surgery. The study revealed that an index complication increased costs by

TABLE 3. **Univariate analysis assessing outcomes**

	Hospital LOS, days			Time to return of bowel function, days			Postoperative ileus			Readmission		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Naloxegol vs. Alvimopan	1.16	1.04, 1.28	0.007	0.83	0.69, 0.99	0.04	1.74	0.84, 3.59	0.14	1.50	0.80, 2.84	0.21
Age	1.01	1.00, 1.01	0.005	1.00	0.998, 1.01	0.19	1.03	0.99, 1.06	0.14	0.99	0.96, 1.01	0.41
Female	0.97	0.88, 1.07	0.51	1.05	0.91, 1.22	0.48	1.22	0.61, 2.44	0.57	1.80	1.02, 3.16	0.04
BMI	0.99	0.99, 1.01	0.46	1.01	0.996, 1.02	0.18	0.94	0.88, 1.01	0.08	1.01	0.95, 1.06	0.81
Prior abdominal surgery	1.13	1.03, 1.23	0.008	1.14	0.99, 1.30	0.06	0.67	0.36, 1.25	0.21	1.07	0.63, 1.83	0.80
Prior radiation therapy	1.34	1.19, 1.52	< 0.001	1.08	0.89, 1.32	0.43	2.52	1.08, 5.87	0.03	1.34	0.61, 2.95	0.46
CCI	1.04	1.02, 1.06	< 0.001	1.02	0.98, 1.05	0.37	1.15	0.98, 1.34	0.09	1.05	0.92, 1.20	0.46
History of diabetes	1.05	0.93, 1.18	0.47	1.02	0.85, 1.24	0.81	1.20	0.50, 2.87	0.69	1.78	0.89, 3.58	0.11
Ecog Grade 2 vs. Grade 1	1.09	0.99, 1.19	0.07	1.00	0.88, 1.15	0.97	0.99	0.52, 1.87	0.97	1.33	0.77, 2.30	0.31
Ecog Grade 3-5 vs. Grade 1	1.21	1.06, 1.38	0.005	1.12	0.91, 1.37	0.29	0.67	0.22, 2.05	0.48	1.25	0.53, 2.90	0.61
Robotic vs. open	0.81	0.74, 0.88	< 0.001	0.79	0.69, 0.89	< 0.001	0.86	0.47, 1.60	0.64	1.59	2.65, 0.07	0.07

LOS = length of stay; BMI = body mass index; CCI = Charlson Comorbidity Index; OR = operating room; CI = confidence interval

$9,262 and a readmission increased costs by $20,697. In addition, each complication increased the LOS by 4 days. Gastrointestinal complications were the fourth most costly complications assessed.[9]

ERAS protocols have gained interest in major abdominal surgeries, such as cystectomy, in recent years. These protocols have emphasized limitations on narcotic use, early oral feeding, regional anesthesia, and use of mu-opioid antagonists. High quality evidence suggest that these standardized, multidisciplinary approaches to perioperative and postoperative care are efficacious in reducing complications, hospital LOS, and as a result, overall cost burdens to the healthcare system.[10,11] One important component of ERAS protocols is the administration of a mu-opioid antagonist, which aims to peripherally block the effects of opioids that may be administered during anesthesia or postoperatively, in an attempt to reduce the negative effects of narcotics on bowel function. Alvimopan is a mu-opioid antagonist that was established as an effective option in reducing postoperative ileus and hospital LOS at the time of cystectomy. This was best described in a multicenter randomized-controlled study by Lee et al that reviewed 277 patients who underwent radical cystectomy. Patients were randomized to alvimopan or placebo in a modified intention-to-treat analysis and the primary outcome was time to upper and lower gastrointestinal recovery. The study found that the alvimopan cohort experienced quicker gastrointestinal recovery, shorter mean hospital LOS and fewer episodes of postoperative ileus.[5] The results of this study led to increased use of alvimopan in the setting radical cystectomy. This was confirmed by a study that reviewed a large US database that included 200 hospital and 7472 patients who underwent cystectomy. The purpose of the study

TABLE 4. **Multivariable analysis assessing outcomes**

	Hospital LOS, days			Time to return of bowel function, days			Postoperative ileus			Readmission		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Naloxegol vs. Alvimopan	1.37	1.17, 1.61	< 0.001	0.86	0.70, 1.06	0.15	1.60	0.48, 5.31	0.44	1.22	0.54, 2.74	0.63
Age	1.01	1.00, 1.01	0.006	1.0	1.00, 1.01	1.31	1.02	0.98, 1.06	0.33	1.01	0.97, 1.05	0.71
BMI				1.01	1.00, 1.02	0.18	0.94	0.87, 1.02	0.13			
Robotic vs. open	0.71	0.65, 0.79	< 0.001	0.80	0.70, 0.92	0.001	0.69	0.33, 1.45	0.33	2.42	1.05, 5.57	0.04
Prior abdominal surgery	1.08	0.98, 1.19	0.12	1.09	0.95, 1.25	0.22	0.53	0.26, 1.07	0.07			
Prior radiation therapy	1.28	1.13, 1.45	< 0.001				2.46	1.03, 5.90	0.04			
Ecog Grade 2 vs. Grade 1	1.07	0.97, 1.18	0.17	0.96	0.84, 1.10	0.57						
Ecog Grade 3-5 vs. Grade 1	1.20	1.04, 1.39	0.01	1.11	0.90, 1.37	0.31						

LOS = length of stay; BMI = body mass index; OR = operating room; CI = confidence interval

was to assess the utilization of alvimopan throughout the US. During a time period of 3 years, the use of alvimopan increased from 35% to 59% and its use was associated with a decrease in development of overall complications and hospital LOS.[7] Similarly, in our study alvimopan use was associated with reduced hospital LOS and lower incidence of postoperative ileus, as well as expedited return of bowel function.

Though the use of alvimopan has increased since it was approved by the FDA in the context of cystectomy, costs of the drug are not insignificant. Up until very recently, this medication was not available as a generic medication. Around the time of its approval by the FDA in 2008, each pill was around $60 and because the medication is typically continued until patients experience a return of bowel function, its costs can accumulate to around $1,000 for each patient.[12] More recently, its cost has increased significantly, to around $190 per capsule, which could result in average costs of around $3,000 for an individual's care after cystectomy.[13] As a result, cost-conscious surgeons turned to naloxegol, a drug in the same class of mu-opioid receptor antagonist, that is available at a much lower cost than alvimopan, where the cost per tablet is around $13.[14] Its use was assessed in a single-center study and the results were similar to this study. The study did not compare objective measures of return of bowel function outcomes between the cohorts, but found that there was no significant difference in the hospital LOS and incidence of postoperative ileus in patients who received either alvimopan or naloxegol.[8] In our study, we similarly found no difference development of postoperative ileus, as well as no difference in return of bowel function. However, hospital LOS was longer in the naloxegol group. It is likely that factors outside of gastrointestinal outcomes contributed to this difference, such as surgeon preference.

Limitations of this study include its retrospective, non-randomized nature. It would be helpful to explore this comparison and confirm this study's findings with future studies in a prospective, randomized manner. In addition, perioperative protocols have varied throughout the duration of the study and some of these variables were not consistently available to compare between cohorts. These include perioperative fluid management, amount of narcotics used during the hospital stay, assessment of surgical difficulty, and patient activity performance during the hospital stay. Additionally, 7 main surgeons were included

in analysis, who have different preoperative and perioperative preferences despite using a common pathway. Also, one of the major factors that can contribute to postoperative gastrointestinal outcomes, opioid use, was not available for some patients due to the multiple electronic medical records used in the timespan of this study. Despite these limitations, this study provides a robust comparison of the objective outcomes between naloxegol, alvimopan and control patients who underwent cystectomy. These findings support the preferential use of naloxegol over alvimopan, so long as dramatic price discrepancies exist between the two products.

Conclusions

Alvimopan and naloxegol are mu-opioid antagonists that can be used at the time of major surgeries, such as cystectomy, to expedite return of bowel function and mitigate the risk of postoperative ileus. We observed no difference in objective measures of return of bowel function, development of postoperative ileus, or complications according to mu-opioid antagonist choice, but experimental data are needed to confirm these findings. Nevertheless, this study forms the basis for the preferential use of naloxegol over alvimopan so long as substantial pricing gaps exist. □

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