Examining the impact of postoperative opioid use on length of hospital stay following radical cystectomy

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Cite as: Kim SSY, MacNevin W, Rendon RA, et al. Examining the impact of postoperative opioid use on length of hospital stay following radical cystectomy. *Can Urol Assoc J* 2023 March 20; Epub ahead of print. http://dx.doi.org/10.5489/cuaj.8167

Published online March 20, 2023

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ABSTRACT

Introduction: Radical cystectomy is associated with high rates of morbidity, prolonged hospital stay, and increased opioid use for postoperative pain management; however, the relationship between postoperative opioid use and length of stay remains uncharacterized. This study serves to investigate the association between postoperative opioid use and length of hospital stay after radical cystectomy. The relationship between patient and surgical factors on length of stay was also characterized.
Methods: We retrospectively reviewed all patients between 2009 and 2019 who underwent radical cystectomy at our institution. Patient and perioperative variables were analyzed to determine the relationship between postoperative opioid use and length of stay using multivariable linear regression analysis.
Results: We identified 240 patients for study inclusion with a median age of 70.0 years. Median length of hospital stay was 10.0 days, with median daily mg morphine equivalent use of 57.5 for

KEY MESSAGES

- Increased daily morphine equivalent use, prior pelvic radiation, postoperative ileus, and higher Clavien-Dindo grade complications during admission after radical cystectomy were associated with increased length of stay.
- Median length of stay increased by 1 day for each increase in daily morphine equivalent use of 13.2 mg.
- Non-opioid-based pain management approaches may be effective in reducing length of stay after radical cystectomy.

patients. Daily mg morphine equivalent use was significantly associated with an increased length of stay, as were previous pelvic radiation, postoperative ileus, and higher Clavien-Dindo grade complication during admission (all $p<0.05$). Median length of stay increased by one day for each increase of 13.2 daily mg morphine equivalents received.
Conclusions: Increased daily opioid use was associated with increased length of hospital stay after radical cystectomy. Non-opioid-based pain management approaches may be effective in reducing length of stay after radical cystectomy.

INTRODUCTION

Radical cystectomy (RC) with urinary diversion is a standard of care treatment for treatment of patients with muscle-invasive bladder cancer (MIBC) and those with non-MIBC disease who are refractory to other bladder preserving therapies[1]. As RC is a major operation, there is a high level of associated morbidity and mortality, with an overall complication rate of approximately 34% and an average length of stay (LOS) in hospital of 10.75 days[2-5]. Prolonged return of bowel function and achieving adequate pain control are factors contributing to this increased LOS and serve as main barriers to discharge[4-5].

Due to the complexities involved with RC, pain management after RC remains a challenge. Although enhanced recovery after surgery (ERAS) care pathways have been implemented to optimize perioperative care and reduce opioid analgesia use, opioid-based pain management strategies are often still required post-operatively[7]. Furthermore, in the RC patient population, increased opioid use in the post-operative period has been shown to lead to decreased gastric motility and post-operative ileus (POI)[7,8]. Despite this, there remains a paucity of literature on the impact of post-operative opioid use and LOS in this patient population. Herein, we investigated the relationship between post-operative opioid use and LOS of patients recovering from RC.

METHODS

Study design and population

After obtaining institutional research ethics board approval, all patients who underwent open RC for bladder cancer at the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, between January 2009 - December 2019 were retrospectively reviewed. Patients undergoing RC for non-malignant causes were excluded. Seven surgeons performed RC surgery in this patient group. At our institution, a standard ERAS protocol was not initiated during the study time frame.

Patients were classified as having prior opioid use if they were prescribed and filled prescriptions for daily opioid analgesia during the 180 days preceding their operation[9]. The use of pain management adjuncts such as transversus abdominis plane (TAP) blockade or epidural anesthesia was administered based on surgeon and anesthesiologist's preference. Patient

assessment by the Acute Pain Service (APS) for pain control recommendations and/or consideration for patient-controlled analgesia (PCA) was coordinated based on the pre-operative assessment or inadequate post-operative pain control. Nasogastric (NG) tubes were placed for post-operative nausea or clinical indications of ileus. Ileus was defined as a failure to progress to a solid diet by the 7th post-operative day or insertion of a NG tube. First day of post-operative flatus or bowel movement was used to indicate return of bowel function. Post-operatively, patients were initially started on a fluid-based diet and were progressed to a solid diet once passing flatus. Complication rate was assessed through examination of a 90-day post-operative time period.

Data collection

Data was collected from the study population through review of their electronic medical record (EMR) which included patient demographic information, operative reports, post-operative inpatient progress notes, and their medication administration record (MAR). All routes of opioid use were recorded for each patient during their hospital stay and were converted into milligram oral morphine equivalent (MME) doses for analysis.

Statistical analysis

Patient demographic and surgical factors were expressed as frequencies and percentages and were analyzed using chi-square analysis, Mann-Whitney U tests, and Kruskal-Wallis tests as appropriate. Multivariable linear regression analysis was used to determine the relationship between patient and surgical factors and LOS. Variables included in the regression analysis were determined based on literature review of patient risk factors associated with prolonged LOS and return of bowel function[10-12]. The variables included were: age, sex, daily MME use, BMI, prior opioid use, prior pelvic radiation, prior neoadjuvant chemotherapy, T stage, post-operative ileus, year of operation, analgesic adjuncts, non-opioid analgesic use, and highest Clavien-Dindo grade during admission. A 95% confidence interval was used and the significance threshold was set at p=0.05.

RESULTS

Patient population

Two hundred forty patients were included in the study with 81.3% (n = 195/240) being male (Table 1). The median age was 70.0 [Minimum, Maximum] [35, 88] years and median BMI was 27.3 [16.6, 45.4]. Most patients had clinical stage T2 bladder cancer (51.7%, n = 124/240) with 37.5% (n = 90/240) of patients having neoadjuvant chemotherapy and 3.8% (n = 9/240) receiving prior pelvic radiation therapy. Twenty-four patients (10.0%) were noted to have a history of prior opioid use. Ileal conduits were created in 85.4% (n = 205/240) of patients, with a median operative time of 178 [100, 469] minutes. Post-operatively, the median LOS was 10.0 [4, 68] days and time to first flatus was 4.0 [1, 10] days.

Post-operatively, 10.8% of patients (n = 26/240) required takeback operations due to complications. Eleven (42.3%) of these involved exploratory laparotomy with lysis of adhesions, bowel resection, or revision of the urinary diversion. Fascial dehiscence repair (19.2%, n = 5/26) and stent repositioning or looposcopy (38.5%, n = 10/26) were other procedures undergone by patients requiring takeback operations. NG tube placement was required in 89 patients (37.1%), and total parenteral nutrition (TPN) was given in 56 patients (23.3%). The majority of operations in our cohort were performed by two surgeons (89.58%). Surgeon involvement and the surgeon's case volume in our cohort did not impact daily MME dose ($p = 0.709$), LOS ($p = 0.559$), day of first flatus ($p = 0.205$), or ileus ($p = 0.857$).

Postoperative pain management

For adjunct pain control, 54.6% (n = 131/240) of patients received bilateral TAP blocks intraoperatively. For non-opioid pain management, all patients received regularly scheduled acetaminophen post-operatively (Table 2). Subcutaneous and oral forms of morphine and hydromorphone were used for opioid-based pain control with a median daily MME dose being 57.5 mg [0.00, 598.3]. The use of pain control adjuncts (ie. TAP blocks, epidural use) was not significantly associated with LOS ($p = 0.439$) or MMEs required ($p = 0.742$) when compared to patients who did not receive these adjuncts. Similarly, there was no statistically significant difference in LOS or daily MME use in patients who received additional non-opioid analgesics beyond scheduled acetaminophen. The APS was consulted for pain management recommendations in 17.1% (n = 41/240) of cases, with patient-controlled anesthesia (PCA) being utilized for 27 patients (11.3%). Patients with prior opioid use were more likely to require APS involvement (25.0% vs 9.72%, $p < 0.005$) and had increased daily MME use (69.27 ± 49.66 mg vs 56.21 ± 64.73 mg, $p = 0.042$).

Increased daily MME use was correlated with prolonged LOS ($\rho = 0.297$, $p < 0.005$), younger patient age ($\rho = 0.268$, $p < 0.005$), increased BMI ($\rho = 0.166$, $p < 0.05$), prior opioid use ($\rho = 0.158$, $p < 0.05$), prolonged time to first flatus ($\rho = 0.144$, $p < 0.05$), and having a higher Clavien-Dindo grade ($\rho = 0.137$, $p < 0.05$).

Patient and surgical factors and length of stay

In multivariable linear regression, prior pelvic radiation, post-operative complications during admission, ileus, and daily MME use were significantly associated with increased LOS. These factors were able to account for 69.0% of the variance in LOS ($F(4,147) = 79.54$, $p < 0.01$, $R^2 = 0.690$) (Table 3). A 1 day increase in LOS was seen with an increase of 13.2 daily MMEs. Post-operative ileus was associated with an increase in LOS by 6.64 days in the model.

Patient and surgical factors and time to first flatus

The median time to first flatus was 4.0 (IQR: 2) days. Multivariable linear regression analysis was not significant for predicting increased time to first flatus using the variables of age, sex, BMI, prior pelvic radiation, daily MME use, LOS, APS involvement, and PCA use. Patients with prolonged return of bowel function requiring NG tube placement had a median LOS of 10.00 (IQR: 6) days compared to 9.00 (IQR: 7) days for those not requiring a NG tube, although this finding was not statistically significant.

DISCUSSION

Radical cystectomy is associated with high levels of morbidity and mortality and patients face multiple barriers and surgical milestones to meet prior to discharge[2]. For the patient recovering from RC, pain management and delayed return of bowel function are main challenges with POI being the most common reason for prolonged hospital stay[13,14]. This is complicated by the role of opioid analgesia being a mainstay of treatment for acute pain management after RC, as increased opioid usage has been shown to increase hospital LOS and has been associated with decreased gut motility and POI[7,8]. Therefore, ensuring effective pain relief while avoiding POI becomes a critical challenge in the post-operative period. To address this need, ERAS care pathways in RC have been shown to reduce post-operative morbidity and improve return of bowel function while reducing LOS[15,16]. Despite this, the impact of opioid use on LOS has not yet been fully explored. Our study served to examine the relationship between post-operative opioid use and LOS in patients undergoing RC, while also examining the association between patient and surgical factors and return of bowel function.

For post-operative adjunct pain management, TAP blocks have been shown to be effective in RC for decreasing opioid use, reducing length of stay, and reducing post-operative complications[19]. In our study, surgeons opted to use intraoperative TAP blocks approximately 50% of the time with no significant difference in MME use or LOS. This is likely attributed to surgeon preference and the recent adoption of TAP blockade use in ERAS care plans when compared to our data which was collected over the past decade[19,20]. Patients with prior opioid use required increased opioid-analgesia and were more likely to have APS involvement and PCA use to optimize their pain control. This highlights the importance of proper pain management in opioid tolerant RC patients in the post-operative period as there was no significant difference in LOS between these groups with proper intervention. Furthermore, the appropriate use of post-operative opioid prescribing is especially important as overprescribing has been shown to place patients at risk for problematic use and dependence[18,21].

LOS was best predicted by daily MME use, highest Clavien-Dindo grade complication during admission, ileus, and the presence of prior pelvic radiation. Our patient cohort had an increased median LOS when compared to the literature (13.45 days vs 10.75 days)[5]. This may be due to sub-optimal pain control, as there was increased daily MME use in our cohort, comparable to the literature for RC patients using non-ERAS care pathways[18,19]. Furthermore, in

our cohort, 10.8% of patients required an additional takeback procedure in the post-operative period, which may have contributed to the increased LOS in our cohort. Recently, implementation of a reduced opioid utilization protocol has shown success in RC by reducing opioid use by approximately 80% without compromising pain control[18]. From this, effective pain management strategies focused on reducing opioid analgesia may be effective in reducing LOS and the costs associated with a prolonged admission[13,18,20].

Clavien-Dindo grade, a specifier for surgical complications, increased LOS in our model by 5.9 days for every increase in grade during admission. Clavien-Dindo grade has been analyzed in RC studies investigating post-operative morbidity and has been shown to be strongly associated with prolonged hospital stay[22]. Post-operative complications requiring additional operations in our study primarily involved bowel resection, urinary diversion revision, and ureteric stent repositioning procedures. Our rate of complications requiring additional procedures during the post-operative period (10.8%) were comparable to RC studies utilizing ERAS pathways (14.0%)[4,6]. Takeback operation type was not significant for differences in LOS or daily MME use. Prior pelvic radiation therapy was shown to increase LOS in our model by 22.4 days if present. Although similar urological studies have not shown prior pelvic radiation therapy as a factor associated with increased LOS or post-operative complications, radiation therapy has been shown to adversely affect the technical aspects of surgery due to obliteration of surgical planes which may increase patient morbidity, in addition to impaired healing in radiated tissues[6,23,24]. Additional studies analyzing the impact of prior radiation therapy on LOS in the post-operative RC population are required to further characterize this association.

The pathophysiology and risk factors for post-operative ileus is complex and multifactorial, based on the individual patient and perioperative factors[25,26]. In our study, the average time to first flatus was similar to comparable RC studies, and prolonged time to first flatus was associated with increased MME use[27]. From this, strategies to reduce opioid use to facilitate earlier return of bowel function can be beneficial for the patient while also reducing hospital operative costs[13,17].

There are several limitations to this study that warrant discussion. This study was retrospective and thus it is not possible to determine all the factors associated with both increased MME and LOS. Some variables that may impact the post-operative course were not able to be captured in our database such as involvement of physiotherapy, timing of patient ambulation, or the amount of pro-motility agents administered. Second, this study was carried out at a single institution. Due to this, institution specific factors and treatment preferences may limit generalizability of these findings to the RC population as a whole. Our study also exclusively focused on open RC procedures, therefore generalization of our results to the robotic or laparoscopic RC patient group may be limited where one of the touted benefits of minimally invasive surgery is decreased post-operative pain. Additionally, the majority of the patients underwent ileal conduit urinary diversion as opposed to neobladder or cutaneous urostomy which may limit the applicability of the results to patients with ileal conduits. Finally, subjective pain

measures were not utilized in this study to determine effective pain control or to trigger APS involvement, therefore, implementing subjective pain measures may be beneficial to better characterize post-operative pain and dictate treatment[7]. Despite these limitations, this study served to characterize the impact of post-operative opioid pain management on LOS for RC patients while highlighting the importance of effective pain control strategies.

CONCLUSIONS

Herein we found that increased daily opioid use was associated with increased LOS after RC. Protocols aimed at reducing post-operative opioid utilization may serve to accelerate the in-hospital recovery of patients undergoing RC.

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FIGURES AND TABLES

Table 1. Patient demographic, surgical, and perioperative factors	
Patient demographics (N=240)	**Frequency (%)**
Gender	
Male	195 (81.3)
Female	45 (18.7)
Prior IBD/Crohn's	3 (1.2)
Prior IBS	1 (0.4)
Prior laxative use	31 (12.9)
Prior opioid use	24 (10.0)
Neoadjuvant chemotherapy	90 (37.5)
Prior pelvic radiation therapy	9 (3.8)
Clinical T stage	
Tis/Ta	14 (5.83)
T1	67 (27.9)
T2	124 (51.7)
T3	13 (5.4)
T4	10 (4.2)
Missing	12 (5.0)
Surgical factors (N=240)	**Frequency (%)**
Diversion type	
Ileal conduit	205 (85.4)
Neobladder	26 (10.8)
Cutaneous ureterostomy	9 (3.8)
Postoperative factors (N=240)	**Frequency (%)**
Highest Clavien-Dindo during admission	
Grade 0	81 (33.8)
Grade 1	41 (17.1)
Grade 2	74 (30.8)
Grade 3	25 (10.4)
Grade 4	14 (5.8)
Grade 5	5 (2.1)
Takeback OR required	26 (10.8)
NG tube required	89 (37.1)
TPN required	56 (23.3)

Table 2. Overview of perioperative pain management approaches	
Perioperative pain management (N=240)	**Frequency (%)**
Acute pain service involvement	41 (17.1)
Patient controlled analgesia use	27 (11.3)
Adjunct pain control procedures	
None	106 (44.2)
Bilateral TAPb	131 (54.6)
Epidural	2 (0.8)
Bilateral TAP block + epidural	1 (0.4)
Non-opioid pain medications ordered	
Acetaminophen	211 (87.9)
Acetaminophen + ibuprofen	23 (9.6)
Acetaminophen + ketorolac	5 (2.1)
Acetaminophen + ibuprofen + ketorolac	1 (0.4)

Table 3. Multivariable linear regression model of post-operative length of stay after radical cystectomy			
Variable	**β**	**95% CI**	**p**
Daily morphine equivalents	0.076	0.071–0.081	<0.001
Highest Clavien-Dindo classification during admission	5.98	4.83–7.13	<0.001
Prior pelvic radiation therapy	22.4	16.6–28.2	<0.001
Ileus	6.64	4.36–8.93	0.004
Age	1.14	0.651–1.63	0.791
Sex	1.00	0.511–1.49	0.962
BMI	0.996	0.507–1.48	0.929
History of neoadjuvant xhemotherapy	0.977	0.488–1.47	0.633
T stage	0.974	0.485–1.46	0.581
Prior opioid use	0.938	0.449–1.43	0.193
Adjunct analgesia (e.g., TAP blockade)	1.05	0.561–1.54	0.311
Non-opioid analgesia	1.02	0.531–1.51	0.677