Enhanced recovery after cystectomy in patients with preoperative narcotic use

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Abstract

Introduction: The aim of this study was to evaluate the outcomes of radical cystectomy with an enhanced recovery after surgery (ERAS) protocol in patients with a history of chronic preoperative narcotic use compared to narcotic-naive patients.

Methods: We identified 553 patients who underwent open radical cystectomy with ERAS. Preoperative narcotic use was identified in 34 patients who were then matched to 68 narcotic-naive patients. Postoperative outcomes, opioid use, and visual analog scale (VAS) pain scores were analyzed and compared. All routes of opioid use were recorded and converted to a morphine equivalent dose (MED).

Results: Patients with preoperative narcotic use reported higher median VAS pain scores per day (postoperative day [POD1]: 5.2 vs. 3.9, p=0.003; POD2: 5.1 vs. 3.6, p<0.001; POD3: 4.6 vs. 3.8, p=0.004) and used significantly more opioids (median MED) per day (POD1: 13.2 vs. 10.0, p=0.02; POD2: 11.3 vs. 6.4, p=0.003; POD3: 10.2 vs. 5.0, p=0.005) following surgery. Preoperative narcotic users were noted to have a significantly higher incidence of 90-day re-admissions (41.2% vs. 20.6%, p=0.03). There was no difference in median hospital stay (4 vs. 4 days, p=0.6), 30- or 90-day complications (64.7% vs. 60.3%, p=0.8 and 82.4% vs. 75.0%, p=0.4, respectively) or gastrointestinal complications (29.4% vs. 26.5%, p=0.8), including postoperative ileus (11.8% vs. 20.6%, p=0.2).

Conclusions: Patients with preoperative narcotic exposure report higher pain scores and require more opioid use following radical cystectomy with ERAS and are more likely to be re-admitted within 90 days. However, there was no observed difference in hospital stay or complications.

Introduction

With an estimated 81 400 new cases diagnosed in 2020, bladder cancer is one of the most common malignancies in the U.S. Moreover, 17 980 patients were estimated to die from bladder cancer in 2020, making it one of the most lethal urological diseases.[1] Radical cystectomy (RC) with urinary diversion is the gold standard management for patients with muscle-invasive or high-risk non-muscle-invasive disease. RC is a morbid procedure with historical early complication rates of up to 67% and length of stay of up to 9–11 days.[2,3] The perioperative management of patients undergoing RC is complex and has seen major improvement in recent years owing to the increased acceptance of enhanced recovery after surgery (ERAS) protocols.[4] We have previously shown the benefit of an ERAS protocol in reducing length of stay without an increase in complications or re-admission rates.[5]

ERAS protocols are multimodal pathways that streamline all elements of perioperative care, including pre, intra, and postoperative interventions. A major focus is on the minimization of narcotic pain management and the use of μ-opioid antagonists to accelerate gastrointestinal recovery.[6] As we strive to improve ERAS protocols and subsequent outcomes, we must target all modifiable factors and better understand non-modifiable ones.

In 2017, the U.S. Department of Health and Human Services declared an opioid epidemic.[7] Over two million patients abuse opioids yearly, with an annual incidence of more than 200 000 new users and 16 000 deaths from opioid overdose.[8] The crisis is widespread and affects many patients undergoing urological procedures, including RC. The efficacy of modern treatment practices on patients with a history of preoperative narcotic use needs to be better understood.

In this study, we investigate the effect of preoperative narcotic use on outcomes in patients undergoing RC with ERAS.

Methods

Study population

Using our prospectively maintained, institutional review board-approved bladder cancer database, we identified all patients with preoperative narcotic use who underwent open RC, pelvic lymph node dissection, and urinary diversion for urothelial carcinoma with intent to cure from June 2012 to June 2017 — the initial five years after implementation of our ERAS protocol. Preoperative narcotic users were defined as those having an active prescription for narcotics for ≥30 days prior to surgery. Narcotic users were identified through preoperative history and physical documentation and meticulous chart review was then performed. Inactive prescriptions and those without verified indications were excluded. Preoperative narcotic users were then matched 1:2 to narcotic-naive patients after controlling for age, gender, pathological tumor stage, and urinary diversion (orthotopic vs. heterotopic).

Pain management protocol

Our ERAS protocol has been previously described.[5] The pain management component of the protocol at the time of the study included intraoperative use of intravenous (IV) acetaminophen and ketorolac, postoperative around-the-clock oral acetaminophen, IV ketorolac, and infusion of ropivacaine via para-incisional subfascial catheters. Oral and IV narcotics were reserved for breakthrough pain only. Oral pain medications were initiated on postoperative day (POD) 0 and patients were converted to oral-only analgesics by POD 3.

Data collection

A dedicated database manager records patient and disease characteristics, complications, and details of re-admissions in our prospectively maintained database. Complications were classified using the Clavien-Dindo system; grade 1 and 2 complications were grouped as "minor," and grades 3–5 were grouped as "major" complications.[3] Complications were also categorized by organ system. Gastrointestinal (GI) complications included diarrhea, bowel obstruction, postoperative ileus (POI), constipation, and GI bleeding. POI was defined as nausea or vomiting with abdominal distension that required cessation of oral intake, nasogastric tube placement, or IV fluid therapy.[6] Infectious complications included urinary tract infection, sepsis, pneumonia, and *Clostridium difficile*. Renal/electrolyte complications included dehydration, electrolyte abnormalities, acute kidney injury, and hydronephrosis.

In-hospital opioid use and visual analogue scale (VAS) pain scores were analyzed retrospectively. Pain scores were averaged from each hour during inpatient hospital stay to calculate a daily average, which was then averaged across the entire hospital stay to achieve a mean VAS score for that hospital admission. Opioid administration by all routes was obtained through meticulous chart review and converted to a morphine equivalent dose (MED). These ratios were obtained through previous studies.[9-11] To avoid overestimation, the lowest epidural-to-intravenous ratios were used.

Data analysis

SAS Version 9.4 (SAS Institute Inc., Cary, NC, U.S.) was used for all data analyses.

Pearson's Chi-squared or Fisher's exact tests were used to examine the association between categorical demographic, clinical, and pathological variables. Kruskal-Wallis test was used to assess differences between continuous variables that were not normally distributed.

All p-values are two-sided and $p<0.05$ was considered statistically significant.

Results

A total of 722 open RCs were performed during the study period. Of these, 553 were for curative intent and enrolled in the ERAS protocol. Preoperative narcotic use was identified in 34 (6.09%) patients. Indications for preoperative narcotic use included chronic arthritic conditions in 16 (47.1%), neurological disease in three (8.8%), urologically related pain in nine (26.5%), and other causes in six (17.6%). Narcotic users were matched to 68 patients with no reported history of narcotic use. Demographic characteristics of the matched cohorts are summarized in Table 1.

Pain scores and in-hospital narcotic use

Preoperative narcotic users reported a higher median VAS pain score than narcotic-naive patients on each postoperative day (POD1: 5.2 vs. 3.9, p=0.003; POD2: 5.1 vs. 3.6, p<0.001; POD3: 4.6 vs. 3.8, p=0.004). VAS pain scores tended to decrease as patients approached discharge from the hospital (Fig. 1). In addition, preoperative narcotic users received significantly more opioids (median MEDs) per postoperative day (POD1: 13.2 vs. 10.0, p=0.020; POD2: 11.3 vs. 6.4, p=0.003; POD3: 10.2 vs. 5.0, p=0.005). Morphine equivalent dosing also tended to decrease as patients approached discharge from the hospital (Fig. 2).

Outcomes

Preoperative narcotic users were noted to have a lower estimated blood loss during their operations (mean 462.3±350.0 ml vs. 523.8±318.4 ml, p=0.04). There was no significant difference in operative time (mean 5.5±1.5 hours vs. 5.6±1.2

Table 1. Clinical and tumor characteristics of 68 narcotic-naive and 34 preoperative narcotic users undergoing radical cystectomy with ERAS after matching

Variable	Narcotic-naive	Narcotic user	
	n=68	n=34	p
Gender, n (%)			1.00
Male	52 (76.5%)	26 (76.5%)	
Median age (IQR)	70.5 (65–79)	71 (64–76)	0.81
Median BMI (IQR)	27.2 (24.9–31)	25.2 (21.5–28.6)	**0.02**
CCI, n (%)			0.36
0	30 (44.1%)	10 (29.4%)	
1	13 (19.1%)	8 (23.5%)	
≥2	25 (36.8%)	16 (47.1%)	
ASA class, n (%)			0.15
1–2	7 (10.3%)	7 (20.6%)	
3–4	61 (89.7%)	27 (79.4%)	
Neoadjuvant chemotherapy, n (%)	26 (38.2%)	11 (32.4%)	0.56
Prior abdominal surgery, n (%)	8 (11.9%)	4 (11.8%)	0.37
Prior pelvic radiation, n (%)	1 (1.5%)	2 (5.9%)	0.21
Tumor stage, n (%)			0.97
<pT3 N0	48 (70.6%)	24 (70.6%)	
≥pT3 N0	11 (16.2%)	5 (14.7%)	
N+	9 (13.2%)	5 (14.7%)	
Diversion type, n (%)			0.97
Orthotopic	43 (63.2%)	22 (64.7%)	
Heterotopic	25 (36.8%)	12 (35.3%)	

ASA: American Society of Anesthesiologists; CCI: Charlson comorbidity index; ERAS: enhanced recovery after surgery; IQR: interquartile range.

hours, p=0.170) or median length of stay (4 days vs. 4 days, p=0.6) between the two groups.

On univariate analysis, we did not find a significant difference in rate of complications between preoperative narcotic users and narcotic-naive patients at 30 days (64.7% vs. 60.3, p=0.8) or 90 days (82% vs. 75%, p=0.4). There was similarly no significant difference in GI complications (29.4% vs. 26.5%, p=0.8) or POI (11.8% vs. 20.6%, p=0.2). Cardiac, pulmonary, and infectious complications were similar between the groups (Table 2) but preoperative narcotic users did have a higher rate of renal/electrolyte-related (41.2% vs. 20.6%, p=0.03) and bleeding-related complications (26.5% vs. 7.4%, p=0.01).

Re-admissions were similar at 30 days (20.6% vs. 13.2%, p=0.3) but preoperative narcotic users did have a higher rate of 90-day re-admissions when compared to narcotic-naive patients (41.2% vs. 20.6%, p=0.03). Complications leading to 90-day re-admissions were stratified based on etiology and are summarized in Table 3. Narcotic users were noted to have a higher proportion of major complications requiring 90-day re-admission compared to narcotic-naive

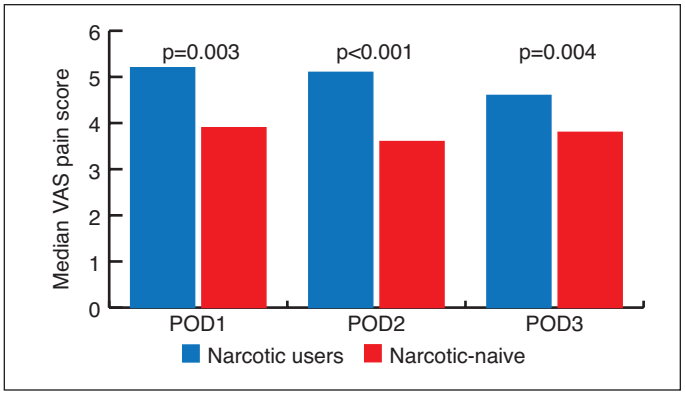

Fig. 1. Postoperative visual analog scale (VAS) pain scores in the two groups. POD: postoperative day.

patients (50.0% vs. 28.6%, respectively, p=0.26), though not significantly so. The most common complications resulting in re-admission among both groups were renal/electrolyte causes (dehydration), followed by infectious, and then GI-related causes.

Discussion

The opioid epidemic exposes urologists to more and more patients with a history of narcotic use before surgery. Chronic preoperative narcotic use has been shown to be associated with higher complications and worse functional outcomes following non-urological surgeries,[12-14] though the data is sparse in urology literature, including for RC. Given the complexity and associated morbidity with RC and urinary diversion, more information in this unique patient subset is needed. Previous studies have shown that ERAS protocols not only decrease hospital stay but also decrease in-hospital pain, narcotic use, and GI complications when compared to traditional recovery protocols.[5,9,15] In a prior report on pain management following RC at our institution, we found that ERAS patients used significantly less opioids (4.9 vs. 20.7 MEDs, p<0.001) and had a lower rate of POI when compared to a pre-ERAS cohort (7.3% vs. 22%, p=0.03).[9]

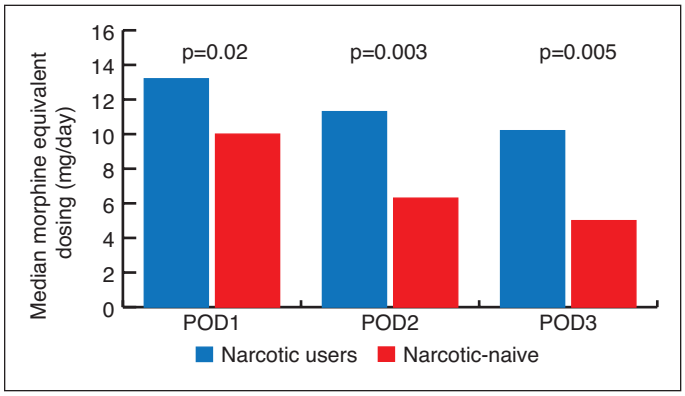

Fig. 2. Postoperative narcotic use in the two groups. POD: postoperative day.

Table 2. Postoperative outcomes (complications and readmissions) of 68 narcotic-naive and 34 preoperative narcotic users undergoing radical cystectomy with ERAS

Outcomes, n (%)	Narcotic-naive	Narcotic user	
	n=68	n=34	p
30-day complications (overall)	41 (60.3)	22 (64.7)	0.8
Low-grade	36 (52.9)	18 (52.9)	0.7
High-grade	5 (7.4)	4 (11.8)	
90-day complications (overall)	51 (75.0)	28 (82.4)	0.4
Low-grade	41 (60.3)	18 (52.9)	0.2
High-grade	10 (14.7)	10 (29.4)	
30-day re-admissions	9 (13.2)	7 (20.6)	0.3
90-day re-admissions	14 (20.6)	14 (41.2)	**0.03**
Gastrointestinal complications*	18 (26.5)	10 (29.4)	0.8
Postoperative ileus	14 (20.6)	4 (11.8)	0.2
Renal/electrolyte complications	14 (20.6)	14 (41.2)	**0.03**
Infectious complications	21 (30.9)	11 (32.4)	1.00
Thromboembolic complications	6 (8.8)	3 (8.8)	1.00
Cardiac complications	5 (7.4)	4 (11.8)	0.4
Pulmonary complications	1 (1.5)	3 (8.8)	0.1
Neurological complications	3 (4.4)	3 (8.8)	0.4

*All complication subtypes are recorded within 90 days following surgery. ERAS: recovery after surgery.

However, we excluded narcotic users in that study. In the current study, our primary goal was to explore the effects of an ERAS protocol in patients with a preoperative history of narcotic use, specifically to determine if they experience the same benefits as those patients without a history of recent narcotic use.

To compare in-hospital narcotic requirements, a MED was used.[11] We found that patients with preoperative narcotic use had significantly more postoperative pain than narcotic-naive patients and required significantly more opioids following surgery. These results are in line with prior studies that suggest opioids may induce hyperalgesia (OIH).[16-18] Chu et al provided evidence for the development of OIH when they tested six patients after one month of oral morphine therapy for lower back pain and found significant hyperalgesia to experimental cold pain.[16] While the methodology of studies testing OIH vary, the mechanism is thought to be due to neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of pronociceptive pathways.[17] Ren et al performed a study in 54 opiate addicts and 46 healthy controls and noted hyperalgesia in the addicts. They also found that pain distress was positively correlated with opiate craving.[18] The association between exaggerated pain responses and drug craving may explain the findings in our study.

Despite the higher pain scores and greater in-hospital opioid use in preoperative narcotic users, there was no significant difference in clinical outcomes aside from renal/electrolyte-related complications and re-admissions within 90 days. There were more high-grade complications leading to re-admission in the preoperative narcotic users compared to narcotic-naive patients but we were unable to identify a significant difference, probably due to the limited sample size of re-admitted patients. The majority of re-admissions in preoperative narcotic users were due to the high-grade renal/electrolyte complications (35.7% compared to 21.4% in the narcotic-naive group). This could be related to the effect of narcotics on the small and large bowel transit that will result in the increase of fluid absorption, third spacing, and fluid/electrolyte imbalance. A recent report showed 142 557 emergency department visits for opioid overdose in the U.S. in 2017 alone,[19] but we were unable to attribute any of our re-admissions to opioid overdose.

Interestingly, we did not find significant differences in GI complications among our two groups. A focus on GI-related complications is particularly important, as the link between narcotic use and bowel function is clear. Previous studies have shown that an increased daily dose of narcotics and increasing days on narcotics both predict POI and length of stay.[10,20,21] The overall GI complication rate in our study was 29.4% in preoperative narcotic users and 26.5% in narcotic-naive patients (p=0.82), while rate of POI was 11.8% and 20.6% (p=0.26) in the respective groups.

Another reason to emphasize GI complications is that prior studies suggest that these represent the most common reason for prolonged length of stay after RC.[22] The median length of stay in both groups was four days and not different from prior reports from our institutional ERAS protocol.[5]

Table 3. Minor and major complications requiring 90-day readmissions by category in 14 narcotic-naive and 14 preoperative narcotic users undergoing radical cystectomy with ERAS

Complication requiring re-admission at 90-days, n (%)	Minor			Major		
	Narcotic-naive	Narcotic users	p	Narcotic users	Narcotic-naive	p
Total	10 (71.4)	7 (50.0)	0.26	7 (50.0)	4 (28.6)	0.26
Gastrointestinal	3 (21.4)	1 (7.1)	0.30	0 (0)	0 (0)	–
Renal/electrolyte	3 (21.4)	3 (21.4)	1.00	5 (35.7)	3 (21.4)	0.42
Infectious	3 (21.4)	2 (14.3)	0.64	1 (7.1)	0 (0.0)	0.33
Thromboembolic	0 (0)	0 (0)	–	1 (7.1)	1 (7.1)	1.00
Cardiac	1 (7.1)	0 (0)	0.33	0 (0)	0 (0)	–

ERAS: enhanced recovery after surgery.

While the previously referenced studies found increased POI and length of stay in narcotic users or those who received greater narcotics in hospital, our patient cohort is unique, as all patients were treated within an ERAS protocol. There are various measures in our protocol that aim to mitigate postoperative stressors, specifically GI-related ones. There is evidence to support many of these measures, including lack of bowel preparation, no nasogastric tube, and early feeding.[23-25] However, the strongest evidence-based intervention in our protocol is the use of pre- and perioperative alvimopan, a μ-opioid receptor antagonist that has been shown to decrease rates of POI, length of stay, and cost after RC.[26,27]

Alvimopan was approved by the U.S. Food and Drug Administration (FDA) in 2008 to accelerate GI recovery following partial large or small bowel resection with primary anastomosis.[28] However, this approval came with a risk evaluation and mitigation strategy (REMS) label warning against its use in chronic narcotic users, defined as those who have been receiving opioids for >7 consecutive days. Thus, the only randomized, controlled trial investigating alvimopan after RC excluded patients who had used narcotics preoperatively.[24]

This REMS label came from preliminary results of a phase 3, double-blind, placebo-controlled study that aimed to evaluate the long-term safety of alvimopan in patients with non-cancer-related. opioid-induced bowel dysfunction (OBD). This study enrolled 805 patients with OBD and randomized them 2:1, with 538 receiving alvimopan 0.5 mg twice daily vs. 267 receiving placebo. The most common adverse events in the study were GI-related, including abdominal pain and diarrhea (40% for alvimopan and 35% for placebo). Serious adverse events occurred in 13% of patients treated with alvimopan and in 11% with placebo, but seven patients (1.3%) in the alvimopan arm suffered from myocardial infarction (MI) compared to none with placebo. The overall rate of serious cardiovascular (CV) events was 2.6% with alvimopan and 1.12% with placebo. All CV events occurred in patients with established or at high risk for CV disease. Still, these findings led to a hold on the drug by the FDA, which was temporary.

Other studies investigating the safety of alvimopan in OBD showed a MI rate of 0.08% with alvimopan compared to 0.38% with placebo, and a rate of 1.18% with alvimopan vs. 0.96% with placebo for all serious CV events.[29-31] The first of these three studies examined 168 patients with OBD (minimum one month of opioid therapy) and found that alvimopan increased the proportion of patients having a bowel movement within eight hours of starting the drug (54%, 43%, and 29% for alvimopan 1 mg, 0.5 mg, and placebo, respectively; $p<0.001$).[29] The latter two studies randomized 1040 patients with OBD to alvimopan or placebo and found a significant increase in the rate of weekly bowel movements ($p<0.001$ for both studies).[30,31]

An FDA panel later declared that the issue of CV safety was not class-specific for μ-opioid antagonists[32] and we have safely administered alvimopan to all patients enrolled in our ERAS protocol, irrespective of prior narcotics use. There was no difference in the cardiac complication rate in this study, at 7.4% for narcotic-naive and 11.8% for preoperative narcotic-exposed patients ($p=0.48$).

While the cause of increased 90-day re-admissions cannot be explained by the results of our study, we do feel our results show that the cumulative effects of the measures included in our ERAS protocol level the playing field for patients with preoperative narcotic use such that they experience similar lengths of stay and complications, importantly GI-related ones, compared to narcotic-naive patients. The greater pain experienced by patients with preoperative narcotic use is an area for improvement and one that we have targeted with multidisciplinary management with our anesthesia colleagues. A recent change to our ERAS protocol since the time of this study has been multimodal prophylactic pain management with oral acetaminophen, celecoxib, and gabapentin for three days prior to surgery. We are also trying to further improve outcomes through preoperative education sessions and potentially more effective therapeutics.

Our study is limited by the retrospective nature of preoperative narcotic use determination. We defined narcotic use before surgery as having an active prescription for ≥30 days, but we do not know how consistently patients were taking narcotics. Similarly, many patients who abuse narcotics may do so without a prescription.[33] A prospective identification of preoperative narcotic users could allow for quantities of preoperative narcotics to be recorded. Still, our results provide a useful reference for surgeons who treat patients with the common scenario of a known but unquantified history of narcotic use prior to surgery.

Another limitation is that VAS scores are currently recorded at inconsistent time intervals and there is no way to collect objective pain information. However, this issue is not limited to our study and must be considered in any study assessing pain management.

The strength of this study is that it presents a group of patients who underwent homogenous cystectomy and received similar perioperative care, with as high as 88% compliance rate to our ERAS protocol.[34] Nevertheless, this sample is not representative of the complete ERAS cohort at our institution and includes only those with preoperative narcotic use and their matched cohort. Moreover, we did not evaluate differences in opioid consumption after discharge from the hospital. Such information will be useful to urologists as we combat the opioid epidemic.

Conclusions

We found that patients with a history of preoperative narcotic use experience more pain and need higher doses of narcotics

following RC. Preoperative narcotic use may increase the risk of 90-day re-admissions but does not affect the rate of GI complications or hospital stay following RC.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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