



## Impact of Enhanced Recovery after Surgery Protocols on Opioid Prescriptions at Discharge after Major Urological Cancer Surgery

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### Abstract

**Introduction:** Enhanced recovery after surgery protocols are designed to limit the use of opioids during inpatient stay to facilitate recovery and early discharge. It is not clear whether the enhanced recovery after surgery related limitations on opioids are associated with opioid prescribing at discharge. We wished to evaluate whether the enhanced recovery after surgery efforts had an impact on opioid prescriptions given after discharge following major urological cancer surgery.

**Methods:** We reviewed the opioid prescription data following hospital discharge after major urological cancer surgery from 2016 to 2018, including cystectomy, renal surgery (total, partial) and prostatectomy. Patient calls and refill requests were recorded for 30 days after discharge. Multivariable analysis was performed to evaluate the effect of various factors on normalized opioid tablets given at discharge.

**Results:** A total of 409 patients met the inclusion criteria, with 207 before and 202 after ERAS protocols. Following enhanced recovery after surgery, potent opioid (oxycodone, hydrocodone) prescriptions decreased by 53% while tramadol use increased by more than four-fold ( $p < 0.001$ ). Reduction in opioid prescriptions was noted for prostatectomy (30%,  $p < 0.001$ ), cystectomy (27%,  $p = 0.02$ ) and all renal procedures (32%,  $p < 0.001$ ) after enhanced recovery after surgery protocol. On multivariable analysis, enhanced recovery after surgery protocol was an independent predictor of reduced opioids given at discharge.

**Conclusions:** Enhanced recovery after surgery protocol implementation was associated with a significant decrease in the opioid prescriptions at discharge after all major urological cancer procedures. Prescribing patterns shifted away from more potent opioids. These findings provide a benchmark for further interventions and reduction in the outpatient opioid prescriptions after open and minimally invasive surgery.

**Key Words:** enhanced recovery after surgery; opioid epidemic; pain management; medication therapy management; analgesics, opioid

### Abbreviations and Acronyms

ERAS = enhanced recovery after surgery

MME = morphine milligram equivalents

Approximately 50 million surgical procedures are performed in the U.S. annually and opioid analgesics are routinely prescribed for postoperative pain control.<sup>1,2</sup> Opioid

use disorder, prescription misuse and deaths resulting from overdose has been a growing problem in the last decade.<sup>3</sup> In 2018 more than 67,000 Americans had died of opioid related

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overdose in 12 months.<sup>4</sup> It is common for patients to have unused opioids after surgery. Patel et al found that 77% of patients reported leftover opioids following urological surgery and only a few patients reported proper disposal.<sup>5,6</sup> In another study as many as 63% of opioid-related deaths were associated with prescription opioid diversion.<sup>7</sup> Even a short exposure to opioids in opioid-naïve patients after minor or major surgery has been associated with de novo habitual or persistent use of opioids in 5% to 30% of patients.<sup>8,9</sup> Therefore, the impetus to reduce dissemination of prescription opioids remains as important as ever.

Early recovery after surgery protocols with standardized perioperative care are comprised of multiple components which are focused on bowel function, venous thromboembolism prevention, analgesia, opioid use and early discharge.<sup>10</sup> One of the essential components of ERAS protocols is to limit the use of opioids during hospital stay to facilitate early return of bowel function and discharge. ERAS protocols promote standardized, systematic use of nonopioid and opioid analgesics but typically do not address the use of opioids after discharge. While the benefits of ERAS protocols on inpatient opioid use, shorter length of hospital stay and cost savings are well documented, the impact of ERAS protocols on opioid prescription at discharge have not been well studied in urological surgery. We sought to determine whether implementation of ERAS protocols had an impact on the opioid prescriptions given at discharge after major urological cancer surgery.

## Materials and Methods

We reviewed the medical records of patients undergoing robotic radical prostatectomy, open or robotic radical nephrectomy, open or robotic partial nephrectomy, and open radical cystectomy from 2016 to 2018, identifying 483 cases. Patients undergoing total or partial nephrectomy and nephroureterectomy were combined into a single renal surgery group (either open or robotic). The main inclusion criterion was the availability of complete opioid prescribing data including the strength, type and dose of the opioid. In all, 74 patients had incomplete information in the discharge documents because they either received no opioid prescriptions or a handwritten prescription or just documentation of chronic opioids without a new prescription which precluded accurate calculation of prescribed dose. Therefore, 409 patients met the inclusion criteria of documented opioid prescriptions at discharge, including those with chronic opioid use.

The various components of our ERAS protocols are similar to the key components outlined by Azhar et al in a systematic review.<sup>10</sup> We have previously demonstrated that ERAS protocol at our center resulted in significant reduction

in length of hospital stay, opioid use and cost, and these benefits were independent of surgical time, body mass index, age or gender.<sup>11</sup> While the focus of this study is on the opioid prescriptions at discharge, we have provided additional details of our ERAS protocols, length of hospital stay and use of opioids before discharge (supplementary tables 1, 1a and 1b, <https://www.urologypracticejournal.com>).

Discharge instructions included use of acetaminophen and/or ibuprofen first before using any opioids for breakthrough pain. The providers who were responsible for patient discharge and prescription included 8 residents and 2 physician assistants working under the supervision of the attending physicians. The type and amount of opioid prescriptions given were based upon the provider's assessment of pain control at discharge. Other medications such as gabapentin, cyclobenzaprine or pregabalin were part of the inpatient ERAS protocol, but not prescribed at discharge. To determine whether patients received any additional opioid refills, we reviewed the outpatient records of patients on ERAS protocols for 30 days after discharge. The office visits, all phone contacts and any outpatient opioid prescriptions were recorded. Due to a change in the medical record system, we could not obtain reliable data on phone calls or outpatient prescription for patients before ERAS protocols.

Primary outcomes of interest for this study were the number (mean±standard deviation) of standardized opioid tablets and the type of medications prescribed at discharge before and after initiating the ERAS protocols. We elected to standardize the opioid dose into standardized tablet counts of hydrocodone-5 mg equivalents because tablets are a more relevant unit for the prescribers. However, the oral MME data has been provided for reference (supplementary table 2, <https://www.urologypracticejournal.com>). Sample size calculation (at alpha 0.05 and 80% power) to detect statistically significant reduction in the mean±SD opioid tablets revealed that the minimum sample size was exceeded for the entire cohort as well as individual procedure except for open cystectomy (supplementary table 2a, <https://www.urologypracticejournal.com>).

Categorical variables were compared before and after ERAS implementation using Chi-square tests and Fisher's exact tests. Continuous variables were compared via t-tests and Wilcoxon rank sum tests. Our outcome of interest, hydrocodone-5 mg tablet equivalents, was distributed on a continuous scale. Multivariable adjustment was performed via linear regression and the adjusted effects with 95% confidence intervals were reported. Analysis was also performed using all available data for each surgical procedure. Statistical software STATA 15.0 was used for analysis and statistical significance was assessed based on alpha of 0.05 and 95% confidence interval of the differences.

## Results

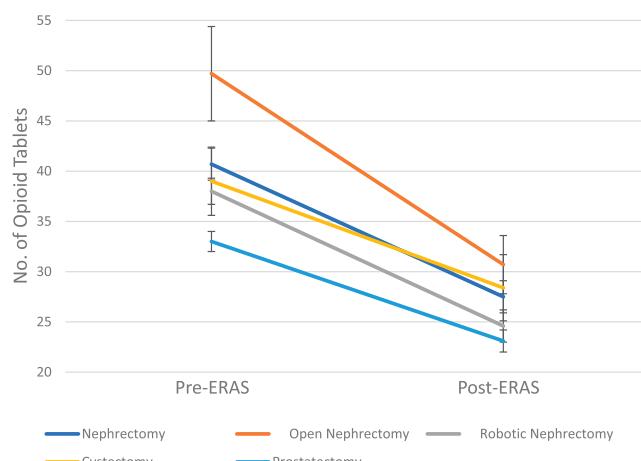
Of the 409 patients, 207 (51%) underwent surgery before ERAS and 202 (49%) after ERAS implementation. Robot-assisted laparoscopic approach was used in 285 cases: 158/285 (55%) before ERAS. Patient characteristics are outlined in table 1. There was no difference in age, gender, race and preoperative opioid use among the groups. There was a significant difference in the type of opioid medications prescribed after ERAS protocol, with tramadol being prescribed at a significantly higher rate than hydrocodone or oxycodone ( $p < 0.001$ ).

There was a significant decline in the mean opioid tablets prescribed at discharge for each procedure after initiating ERAS (fig. 1). For open radical and open partial renal procedures (greater than 90% with flank incision), the mean opioid tablets decreased by 38.2% ( $49.7 \pm 15.4$  vs  $30.7 \pm 18.5$ ,  $p < 0.001$ ) and for robotic renal procedures, the mean decreased by 34.6% ( $37.6 \pm 14.6$  vs  $24.6 \pm 14.3$ ,  $p < 0.001$ ). For patients undergoing prostatectomy, a 30% ( $33.2 \pm 9.1$  vs  $24.3 \pm 8.3$ ,  $p < 0.001$ ) reduction in the mean was noted. Opioid tablets prescribed after cystectomy decreased by 27.2% ( $39.0 \pm 17.1$  vs  $28.4 \pm 12.9$ ,  $p = 0.04$ ). For the entire study group of 409 patients, the mean opioid tablets prescribed decreased by 30% ( $37.3 \pm 15.1$  vs  $26.3 \pm 14.7$ ,  $p < 0.001$ ).

Multivariate analysis was performed for the entire study cohort, and for each surgical procedure individually, including all available variables. After adjusting for age, gender, race and preoperative opioid use, ERAS protocol was an independent predictor with the most significant reduction in opioid tablets given at discharge, followed by type of surgery (table 2). Increasing age was also associated with fewer opioid tablets given at discharge. With open surgery as the reference, minimally invasive surgery was associated with higher reduction rate of opioid prescription. The multivariable analysis for individual procedures is provided in supplementary tables 3 to 5 (<https://www.urologypracticejournal.com>).

**Table 1.**  
Patient characteristics

	No. Pre-ERAS (%)	No. Post-ERAS (%)	p Value
Gender:			
Male	160 (77.3)	143 (70.8)	
Female	47 (22.7)	59 (29.2)	
Race:			0.80
White	187 (90.3)	186 (92.1)	
Black	12 (5.8)	9 (4.5)	
Others	8 (3.9)	7 (3.5)	
Preop narcotics:			0.10
No	195 (94.2)	195 (96.5)	
Yes	12 (5.8)	7 (3.5)	
Opioid prescribed at discharge:			<0.001
Hydrocodone	49 (23.7)	6 (2.9)	
Oxycodone	140 (67.6)	93 (46.0)	
Tramadol	18 (8.7)	103 (51.0)	



**Figure 1.** Reduction in standardized opioid tablets prescribed in patients treated under ERAS protocol for various procedures.

The opioid medications prescribed at discharge included hydrocodone with acetaminophen, oxycodone and tramadol (fig. 2). Before ERAS protocol, 91% of patients received either hydrocodone (24.7%) or oxycodone (67.6%). After ERAS protocol, the use of tramadol increased from 9% to 51% ( $p < 0.001$ ) signifying a substantial trend away from more potent opioids.

A review of outpatient medical records of 202 patients on ERAS protocols identified phone calls from 38 (18.8%) patients (primarily related to the Foley catheter, gastrointestinal issues, bladder spasms, pain and hematuria) of which 13 (6.6%) required opioid refill. All 13 patients requiring additional opioids had undergone either open (8) or robotic renal procedure (5), and 10 of 13 were younger than age 55 years.

## Discussion

Nearly 200 million opioid prescriptions are dispensed per year in the United States.<sup>12</sup> The rate of opioid prescription is the highest among certain specialties including surgery,

**Table 2.**

Regression analysis of difference in opioid (hydrocode 5 mg equivalent) tablets prescribed at discharge, including all procedures

		Univariable Difference (95% CI)	p Value	Multivariable Difference (95% CI)	p Value
No. Gender:					
Female	106	Reference		Reference	
Male	303	-0.07 (-3.59–3.45)	0.970	2.75 (-0.81–6.32)	0.13
Age (for every 1-year increase in age)	62.3 (10.9)	-0.20 (-0.34–0.06)	0.005	-0.17 (-0.30–0.03)	0.01
No. Race:					
White	373	Reference		Reference	
Black	21	0.93 (-6.07–7.93)	0.793	-0.60 (-6.95–5.75)	0.85
Others	15	-1.10 (-9.31–7.12)	0.794	-1.72 (-9.25–5.80)	0.65
No. preop narcotics:					
No	392	Reference		Reference	
Yes	17	9.38 (1.71–17.05)	0.017	4.14 (-3.11–11.4)	0.26
No. procedure type:					
Open renal surgery*	84	Reference		Reference	
Robotic renal surgery*	139	-4.96 (-9.22–0.71)	0.022	-6.85 (-10.86–2.84)	0.001
Robotic prostatectomy	146	-7.05 (-11.26–2.83)	0.001	-10.98 (-15.30–6.67)	<0.001
Open cystectomy	40	-1.07 (-6.98–4.84)	0.723	-4.84 (-10.49–0.80)	0.09
No. ERAS protocol:					
Before	207	Reference		Reference	
After	202	-10.99 (-13.89–-8.10)	<0.001	-12.63 (-15.51–-9.75)	<0.001

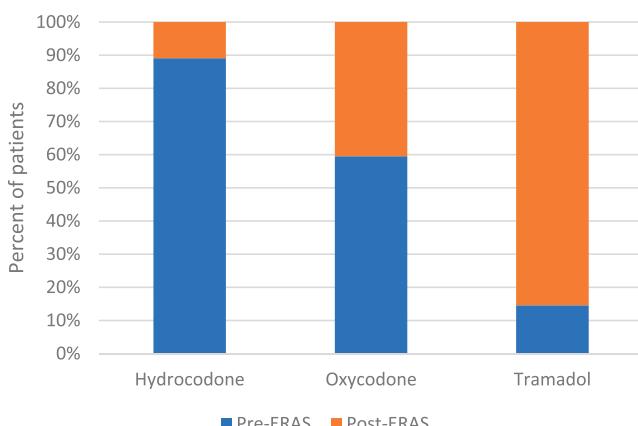
\* Renal surgery includes radical nephrectomy, partial nephrectomy and nephroureterectomy.

accounting for 36.5% of prescriptions.<sup>13</sup> Opioid prescriptions are a major contributor to the opioid abuse epidemic. Nearly 40% of opioid overdose-related deaths involve prescribed opioids.<sup>4</sup> Among patients diagnosed with opiate dependence, 80% received an opioid prescription before their abuse diagnosis and 51% had a family member with an opioid prescription.<sup>14</sup> Two recent studies have brought over-prescribing into stark relief. Theisen et al reported that for 155 patients an average of 39 hydrocodone equivalent tablets were prescribed at discharge, of which 60% remained unused.<sup>15</sup> Raskolnikov et al reported that discharge prescription after renal surgery averaged an alarming 73 hydrocodone equivalent tablets.<sup>16</sup> Davuluri et al evaluated the effect of New York State mandated education on opioid prescriptions and noted no decrease in the opioid prescription rate,

although fewer oxycodone tablets were prescribed.<sup>17</sup> A recent survey of urology trainees carried out by Carpinito et al showed that a significant proportion were continuing to prescribe opioids for relatively minor endoscopic procedures.<sup>18</sup> The contemporary opioid prescribing habits remain quite concerning, prompting the American Urological Association to organize an opioid stewardship summit in 2018.<sup>19</sup> Therefore, it is essential to identify all measures, direct or indirect, that have the potential to reduce opioid prescriptions at discharge.

It is important to make a distinction between inpatient opioids used, which are guided by the ERAS protocol, and opioids prescribed at discharge. While the ERAS protocols typically escalate analgesics, from nonopioids to opioids, during the hospital stay, the ERAS protocols do not address discharge analgesia or opioids. We reviewed several ERAS protocols for abdominal/pelvic surgery from other centers (including various surgical specialties) and did not find specific directions for discharge analgesia or opioids. In our 409 patients undergoing open or robotic surgery, there was a significant 27% to 38% decrease in opioid prescriptions after ERAS implementation. On multivariate analysis ERAS protocol was independently associated with decreased outpatient opioid prescriptions. The largest decrease in prescribed opioids after discharge was noted in the open renal surgery group (38%). The smaller, 27% decrease in opioid prescription in the radical cystectomy group after ERAS was not statistically significant, likely due to the small sample size.

Concerns related to limited prescriptions of opioids include poor pain control, excessive phone calls, and

**Figure 2.** Change in type of opioid medications prescribed at discharge from hospital after implementation of ERAS protocol.

additional requests for refills. While pain scores were not available in our cohort, refill requests for opioids may be used as a surrogate for ongoing pain after discharge. In the ERAS group, only 6% of patients needed additional opioids. These were primarily patients younger than age 55 who had undergone renal surgery. This data identifies a subgroup of patients that could benefit from adjustments in the postoperative analgesic regimen (eg addition of cyclobenzaprine or pregabalin).

A 2019 report by Liu et al on the opioid prescriptions following the implementation of a system-wide ERAS program noted a 33% decrease in opioid prescriptions at discharge after colorectal and hip surgery.<sup>20</sup> A similar spillover effect was described by Howard et al in a 2019 study where an intervention to reduce postoperative opioids for 1 procedure resulted in decreased opioids prescribing for 4 other procedures.<sup>21</sup> Conversely, Gerrish et al noted that while ERAS protocols resulted in shorter hospital stay, these patients were actually prescribed more opioids at discharge than the nonERAS group (61.4 vs 48.4 hydrocodone tablets, respectively).<sup>22</sup>

Others have reported the use of more direct interventions to reduce postdischarge opioid prescriptions. Talwar et al reported on an escalating analgesic pathway to reduce opioid prescriptions after 170 robotic renal and prostate surgeries.<sup>23</sup> Before the study, opioid prescriptions were given to 100% of robotic cases (75–337 MME), which could be reduced or eliminated in 67.7% of the patients. Patel et al implemented a plan to reduce opioid prescriptions after prostatectomy including a discharge sheet, nursing education and standardized prescribing guideline.<sup>24</sup> They noted a reduction in opioid prescriptions from 224 MME to 120 MME (from 45 to 24 hydrocodone-5 mg tablets). The reduction following their directed intervention is similar to the opioid reduction to 23 tablets noted in our prostatectomy patients following ERAS protocol.

A recent study of 244 patients by Lillemoe et al evaluating the effect of ERAS protocol on the outpatient use of opioids following liver surgery (open and laparoscopic) reported outcomes that are similar to our study.<sup>25</sup> Of the patients managed with traditional, nonERAS pathway, 79% received potent opioids (oxycodone, hydrocodone, hydromorphone) and 21% received tramadol. A reversal of this prescribing pattern was noted in the patients managed with ERAS protocol where 26% received potent opioids and 69% received tramadol. Independent predictors of opioid prescriptions included ERAS protocol, preoperative opioid use and open surgery.

To our knowledge, this is one of the few studies of urological surgery evaluating the opioid prescriptions following ERAS. We demonstrated a significant decrease in

opioid prescriptions for open and minimally invasive surgical procedures. The mechanism of the impact of ERAS protocols on post-operative opioids prescriptions is likely multifactorial and in part related to increased awareness and standardization of pain management strategies brought into focus by the ERAS protocols. The enhanced focus of the surgical team, including the discharging providers, on reducing opioid use during inpatient recovery likely translated into fewer outpatient opioid prescriptions and a trend away from potent opioids.

Our study has several limitations that are related to retrospective analysis which can introduce confounders. We could not collect data on the number of tablets used or properly disposed of by the patients. Further, it is possible that the reduction in opioid prescriptions after ERAS was influenced by exogenous factors, such as increased awareness in society and within the medical community. However, some recent studies have reported an increase in post-operative opioid prescriptions, suggesting that there has not been a universal reduction in opioid prescriptions after ERAS.<sup>22,26</sup> Furthermore, the Centers for Disease Control and Prevention has recorded a modest 7.3% decrease in opioid prescriptions per 100 persons between 2017 and 2018 in the United States (and in New York).<sup>27</sup> Therefore, while the exogenous factors could have a partial effect much of the reduction in opioid prescriptions in our study appears to be related to the implementation of ERAS protocols.

While our data demonstrate a reduction in opioid prescriptions given at discharge after implementation of ERAS protocols, recent reports of unused postoperative opioids suggest that further reduction in prescriptions is necessary. Additional efforts such as amending the ERAS protocols to include specific instructions regarding postdischarge pain control and opioid-specific prescription guidelines will be helpful in further reducing the opioid prescriptions and curbing the opioid abuse epidemic.

## Conclusions

A significant decrease in opioid prescriptions at discharge was noted following the implementation of ERAS protocols for open and minimally invasive urological cancer surgery. Bringing a focus on controlling opioid use during inpatient stay was associated with reduction in outpatient opioid prescriptions and a significant shift away from potent opioids. These data provide a benchmark for further interventions to reduce opioid prescriptions after surgery, reduce the potential for chronic abuse by patients, and prevent the dissemination and diversion of unused opioids.

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## Editorial Commentary

The authors should be commended for their efforts in addressing opioid prescribing practices in urology. One area of major concern that was addressed in the discussion is the

fact that prescribing practices may have been impacted by increased awareness about opioid overprescription during the time period of the study. Another concern is the fact that

opioid protocols at discharge were not clearly outlined and were based upon physician discretion. Interestingly, acetaminophen and/or ibuprofen were the recommended first line analgesics for both pre-ERAS and post-ERAS patients, suggesting that an outpatient opioid reduction effort had already been under way prior to the start of inpatient ERAS protocols. Such an effort could potentially have contributed to a significant impact on the outcome of the study, even more so than the ERAS protocols. In any case, this study suggests

that the benefits of ERAS protocols potentially extend beyond the inpatient setting into the outpatient arena. Further examination and standardization of outpatient opioid reduction efforts would be complementary to such inpatient protocols.

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### **Reply by Authors**

We appreciate the comments by Dr. Tseng about the need to address opioid prescribing patterns. It is worth noting that in all pre-intervention and post-intervention studies the potential confounding effect of external factors is always a possibility that cannot be avoided except in a prospective randomized study. The New York State mandatory prescription monitoring program and mandatory opioid prescribing education was initiated in 2013, ie increased awareness campaigns preceded the control (pre-ERAS) group by several years. This, along with a relatively modest decline in opioid prescriptions noted nationwide, would suggest that the role of external factors in our post-intervention group may be minimal. While our discharge instructions have stated the use of nonopiods as first line

analgesics, the opioid prescribing behavior changed significantly only after the implementation of ERAS protocols, even in the absence of standardized prescribing instructions. This phenomenon of spillover effect has been described in other specialties. We agree that it is critically important to continue to utilize all measures, direct or indirect, to control the dissemination of opioids. Based on our current study findings, we have prospectively implemented a direct intervention study entitled “No Opioids PrescriPtions On Discharge after Surgery (NOPIOIDS) (<https://clinicaltrials.gov/ct2/show/NCT04469868>) with the express goal of eliminating opioid prescriptions after major urological surgery.