

**Opioids use after uro-oncologic surgeries in time of opioid crisis**

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**Abstract**

**Introduction:** Recent literature emphasizes how over-prescription and lack of guidelines contribute to wide variation in opioid prescribing practices and opioid-related harms. We conducted a prospective, observational study to evaluate opioid prescriptions among uro-oncologic patients discharged following elective in-patient surgery.

**Methods:** Patients who underwent four surgeries were included: open retropubic radical prostatectomy, robot-assisted radical prostatectomy, laparoscopic radical nephrectomy, and laparoscopic partial nephrectomy. The primary outcome was the dose of opioids used after discharge (in oral morphine equivalents [MEq]). Secondary outcomes included: opioid requirements for 80% of the patients, management of unused opioids, opioid use three months postoperative, opioid prescription refills, and guidance about opioid disposal.

**Results:** Sixty patients were included for analysis. Patients used a mean of 30 MEq (95% confidence interval 17.8–42.2) at home and 80% of the patients used 50 MEq or less. A mean of 40.4 MEq per patient was over-prescribed. Fifty percent of the patients kept the remaining opioids at home, with only 20.0% returning them to their pharmacy. After three months, 5.0% of the patients were using opioids at least occasionally. Three patients needed a new opioid prescription. Forty percent reported having received information regarding management of unused opioids.

**Conclusions:** We found 60% of opioids prescribed were unused, with half of our patients keeping these unused tablets at home. Our results suggest appropriate opioid prescription

amounts needed for urological cancer surgery, with 80% of the patients using 50 MEq or less of morphine equivalents.

## Introduction

Opioid overdose and addiction are two contemporary growing problems in North America. Opioid overdoses killed more people than car accidents in the United States in 2015.<sup>1,2</sup> Canada is less affected but has its share of responsibility being the 2nd largest opioid prescriber.<sup>3,4</sup> In the province of Quebec, the opioid problem remains relatively low compared to the rest of Canada, especially when compared to British-Columbia (9,4 vs 25 opioid-related hospitalizations/100 000 habitants)<sup>5</sup>. Both preventing the problem from worsening and improving the current situation rests in large part with surgeons as regular prescribers of opioids. In Canadian universities, medical students spend an average of 16h class on pain control while veterinary students spend around 87h.<sup>4</sup> Thus, there clearly room for better prevention and education.

Worldwide, opioid prescriptions doubled between 2001 and 2013.<sup>6</sup> This is particularly alarming since overprescribing is one of the most dominant factors influencing the development of opioid addiction.<sup>3,7</sup> It is estimated that opioid naive patients who take a single opioid dose have a 6% chance of becoming addicted after one year and a 3% risk after three years.<sup>8</sup> After minor or major surgery, it is estimated about 5-8% of opioid-naive patients can become addicted.<sup>1,2,6,9</sup> It is also known that the total amount of opioids prescribed is associated with misuse (defined as the use of opioids in a different manner or dose than prescribed by the physician) and need for prescription refills.<sup>10</sup> In 2019, according to a Lancet review on opioid prescriptions after surgery, 67% of patients had an excess of prescribed opioids and 91% kept them at home.<sup>6</sup> Similarly, many studies revealed that unused prescribed opioids represent nearly 50% of the total and less than 10% of those are correctly disposed of.<sup>2,3,9</sup> Among regular consumers, 60% are consuming non-prescribed opioids obtained from a close family member.<sup>11</sup> The World Health Organization indicates that being a family member of someone prescribed opioids is a risk factor for opioid overdose.<sup>12</sup> As physicians, there are actionable factors identified to decrease prolonged opioid use after surgery: the dosage of prescriptions and the duration of the initial prescription are risk factors for opioid abuse. Therefore, the role of physicians, residents, and nurses is of crucial importance.<sup>6,12</sup>

Considering the above information, we believe that there is a lack of local guidelines regarding the correct amount of analgesic opioid medication to prescribe in the post-operative period. In this study focusing on uro-oncologic patients, we evaluated prescribing practices for common operations at our hospital. To do so, we conducted a

prospective observational study to assess how much opioids uro-oncologic patients received after hospital discharge and how much they really used at home.

### Methods

This project was approved by our local ethics committee (2020-4880). In this study, we prospectively enrolled patients having oncologic surgery in Hotel-Dieu de Québec. Patients included in the study were men and women 18-80 years old having one of 4 common urologic cancer surgeries. We selected patients having 4 different surgeries: open retropubic radical prostatectomy (RP), robot-assisted laparoscopic radical prostatectomy (RALP), laparoscopic radical nephrectomy (LRN), or laparoscopic partial nephrectomy (LPN). In our center, every radical prostatectomy includes standard or extended bilateral pelvic lymph nodes dissection. Patients were excluded who chronically took opioids pre-operatively, had an alcohol or drug use disorder, experienced a peri-operative or early post-operative complication (Clavien-Dindo > 2), had another concomitant surgery, or had laparoscopic surgery converted into open surgery.

Our primary outcome was to find the dose of opioids used in oral Morphine Equivalent (MEq) at home after each urologic surgery. MEq is a standardized measure for opioid content corresponding to the equivalent milligrams of morphine. In order to get the equivalent of morphine tablets, a division of MEq value by five is necessary. The secondary outcomes included the dose of opioids required by 80% of patients for each surgery, management of unused opioids, number of patients still consuming opioids 3 months after surgery, number of patients who needed an opioid prescription refill, and the number of patients who had information about opioid disposal.

Participants were met the day before or the day of discharge. We had two clinical nurses who participated subsequently in opportunistic recruitment. No urology resident or attending staff other than the authors were aware of the study to eliminate the Hawthorne effect whereby individuals change prescribing practices knowing they are observed. Three questionnaires were completed during the study. The first questionnaire assessed for demographics immediately after signing the consent form. A second questionnaire was sent 1 month after surgery, in which was included an instruction form to help patients answer questions about the prescribed drug, dose and quantity. Three months after surgery, a third and final form was sent to collect information on their opioid consumption to date and how they disposed of the remaining pills. Patients were contacted if we did not receive their questionnaire 1 month after sending it.

### Results

From October 2019 to August 2020, 77 patients were approached to participate in the study, and 68 patients accepted and were enrolled. Eight were excluded for analysis because of post-operative complications or the absence of follow-up. Fifteen patients had RP, 28 had RALP, 5 had LRN and 11 had LPN. We also included 1 patient who had a

robotic partial nephrectomy (RPN). This group of patients includes patients from 10 urologists. The mean length of stay was 2.1(0.95 SD) days.

Participants were aged between 43 and 84 years old (Table 1). Most of the patients are either married (53.3%) or with a common-law partner (30%). Highest educational attainment included 33.3% with a high school degree, 15.0% with a college degree, 28.3% with a university degree, 16.7% with a professional diploma, 5.0% with a primary degree and 1.7% reported other schooling. Patients' annual incomes were divided as 0-30k (8.3%), 30-50k (38.3%), 50-80k (21.7%), 80-100k (10.0%), > 100k (15.0%) and undeclared (6.7%). Most patients identified themselves as Caucasian (83.3%) and 1.7%, 1.7%, 10.0%, and 3.3% of the patients identified themselves as First Nations, Metis, other, and undeclared.

In the three months before their enrollment, 8.3% of patients had used opioids, but less than once a month. Seven patients (11.7%) reported drinking alcohol every day and 21 patients (35.0%) drinking alcohol weekly. Two patients (3.3%) reported using recreational drugs weekly.

Hydromorphone was prescribed for 53 patients (88.3%), morphine for 2 patients (3.3%) and 4 patients (6.7%) did not take their opioid prescription. In total, 3510 MEq (702 tablets), a mean of 65 MEq (13 tablets) per patient, were prescribed at discharge. At home, patients used a mean of 30 MEq (17.8;42.2, 95% IC) and a median of 15 MEq. Fifty MEq (10 tablets) correspond to the 80<sup>th</sup> percentile of opioids used in our population. When asked to rate their pain control at home, on a scale out of 10, 10 being pain-free, patients rated a mean 8.8/10 (8.2;9.4, 95% CI) compared to a mean of 8.5/10 (7.9;9.2) in hospital. The dose of opioids used at home was not associated with the type of surgery ( $p=0.8$ ), neither the total opioids used including those consumed during hospitalization ( $p=0.68$ ). We did not find a correlation between the length of stay and discharge opioids use (0.09, Kendall Tau b). However, patients who used 27.5 MEq or less during hospital stay were 4.5 times more prone to use no opioid at home ( $p=0.01$ , Bivariate logistic regression). There were no statistically significant association between opioid use after discharge and marital status ( $p=0.3$ ), education ( $p=0.44$ ), annual income ( $p=0.81$ ), ethnicity ( $p=0.54$ ), alcohol consumption before surgery ( $p=0.88$ ), nor pre-operative drug consumption ( $p=0.55$ ).

A total excess of 2220 MEq were prescribed (the equivalent of 444 morphine 5 mg tablets) with a mean of 40.4 MEq per patient. At 1 month postoperative, half of the patients (50.0%) kept their overprescribed opioids at home while only 13.3% returned them to their pharmacy. Others either disposed of them themselves (3.3%), had no excess opioids (10.0%), or did not fill their opioid prescription (10.0%). At 3 months, half of the patients still had excess unused opioids at home (48.3%), while 20.0% of the patients returned them to their pharmacy, 1.7% had given them to someone, 5.0% used them for other reasons, and 15.0% had no excess opioids (Table 3). At 3 months post-operative, 1

patient (1.7%) reported using opioids regularly, 2 patients (3.3%) reported using opioids occasionally, and 3 patients (5.0%) rarely. Three patients (5.0%) needed an opioid refill. Instruction received for management of excess opioids was reported by 26.7% and 40.0% of the patients at 1 month and 3 months, respectively.

### Discussion

Within our sample of uncomplicated oncologic surgeries, we found a mean of 30 MEq (6 tablets) use following hospital discharge. In our sample, the opioid need did not vary significantly according to the surgery. Patients rated good pain control at home with a mean of 8.8/10. Our results suggest that to decrease potential for opioid-related harms, MEq prescribed at discharge for uncomplicated surgeries should be less than 50 MEq (10 tablets of hydromorphone 1 mg or morphine 5 mg), as this dose or less was required by 80% of our patients and only 3 patients (5.0%) needed a new opioid prescription.

Other studies looking at opioid needs after radical prostatectomy found mean patients' requirements between 50.5 to 58.6 MEq.<sup>10,13</sup> According to our results, 80% of our patients would need 50 MEq or less (10 Morphine 5 mg tablets equivalent) after discharge. This is higher opioid requirements than reported by Theisen et al. where 80% of their patients needed between 17 and 23 oxycodone-equivalent (25 to 34.5 MEq) after RP, laparoscopic/robotic nephrectomy, and RALP.<sup>2</sup> However, in-hospital analgesia protocols were different and co-analgesia was not captured in their study, limiting the comparisons. However, these doses are significantly lower than the 100 MEq often prescribed after discharge. We did not find an association between any demographic factors studied and the dose of opioids used. However, Loeb et al. found a higher risk of new chronic opioids use with patients having higher cancer risk, greater comorbidity, unmarried status, and low educational level.<sup>14</sup>

Overall, an excess of 2220 MEq (63.2%) were prescribed in only 60 patients. This dose corresponds to 444 tablets of Morphine 5 mg being potentially available for misuse. These results are similar to 60% and 77% reported by Theisen et al. and Patel et al.<sup>2,10</sup> On the other hand, we found that patients using 27.5 MEq or less during hospital stay were 4.5 times more prone to use no opioid at home ( $p=0.01$ ), so adjusting patients' opioid prescriptions before discharge according to the dose received during hospitalization could be a strategy to reduce opioid overprescription.

We observed half of patients kept the excess opioids at home while only 13.3-20.0% reported having returned them to their pharmacy. These trends were also highlighted by similar studies where 9% of the patients disposed of their excess opioids correctly and 74-92% of the patients reported keeping the excess opioids at home.<sup>10,15</sup> increasing the risks of misuse.<sup>8</sup> The latter phenomenon could also be related to the fact that at 1 and 3 months post-operative, only 26.7 and 40.0% of the patients reported having received information about excess opioid disposal. Evaluating the prolonged use of opioids after surgery, we observed that at 3 months, 3 patients (5.0%) still reported

using opioids regularly or occasionally. This agrees with Brummett et al. who reported 5.9-6.5% new persistent opioids use after major surgery.<sup>16</sup>

Looking at some causes of overprescription and possible improvement strategies, we considered concentrating our attention on different facts. In our university-affiliated centers, prescriptions are often written immediately prior to the surgery using pre-filled prescriptions including 20 tablets of hydromorphone 1 mg (100 MEq). This is a common practice among many surgical specialties. Patient satisfaction and hospital performance are often related to the absence of pain after surgery as a high-stakes indicator.<sup>17</sup> As doctors, we wish to achieve this outcome for our patients, avoiding the inconvenience of returning to the hospital for a prescription refill. Moreover, prescriptions may often be written by residents who were not principally involved in the surgery or peri-operative care, reducing the possibility of individualized prescription adjustment.

The main limitation of the study is the small sample size. We had difficulties enrolling patients because of our opportunistic-based recruitment. Our recruiting nurse worked part-time on the project with a variable schedule and a full-time job as a clinical nurse in the urology department. The COVID pandemic also significantly impacted recruitment possibilities. Nonetheless, our results largely correspond with similar existing literature and can support future prospective studies in the postoperative period. Despite relatively few patients included, it is nonetheless striking that there was an excess of 2220 MEq of prescribed opioids in our study. Extrapolated annually, where greater than 400 of the 4 surgeries included in our study are performed, approximately 14 800 MEq (2 960 tablets) of excess opioids could be available with the potential for abuse.

The lack of control on the co-analgesia was the second limitation. Ziegelmann et al. compared the prescription of opioids in MEq before and after introducing evidence-based guidelines to surgeons for postoperative urologic surgery and found the median MEq prescribed decreased by 33% with refill rates unchanged.<sup>18</sup> Similar results were obtained by Patel et al. where patients decreased opioid use after prostatectomy by 26.5% after implementing an evidence-based co-analgesia interventions.<sup>19</sup> Co-analgesia may even be sufficient to eliminate post-operative opioid use.<sup>20-22</sup> With their protocol, Hallway et al. found high satisfaction and good pain control for 47% of robotic prostatectomy patients with no opioid use.<sup>23</sup>

Other key points to decrease opioid needs include appropriate counseling, pre-operative co-analgesia (gabapentin, acetaminophen with or without nonsteroidal anti-inflammatory drugs), regional or local anesthetic before incision, opioid-free protocol during surgery, and postoperative co-analgesia (ketorolac, gabapentin, and acetaminophen).<sup>24</sup> The Center for Disease Control also suggests reducing opioids use to 3 days or less to reduce the chance of addiction, side effects, and misuses by relatives.<sup>8</sup> Having a shared decision about opioid prescriptions may also play a role in diminishing opioid prescriptions.<sup>6</sup>

**Conclusions**

In our cohort, we found 60% of opioids prescribed were in excess of patient needs. Nearly 50% of our patients kept their unused tablets, probably due to lack of counseling at the hospital discharge. After uncomplicated urologic cancer surgery, patients generally required between 30 to 50 MEq of opioids at home. A reduction and personalization of the dose of opioids prescribed is warranted, while the optimisation of co-analgesia could further decrease opioid requirements. Multidisciplinary consensus meetings for local guidelines and educational meetings for health stakeholders should be considered.

DRAFT

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## Figures and Tables

<b>Table 1. Demographics</b>		
Age, mean	63.2	
	<b>n</b>	<b>%</b>
<b>Surgery</b>		
RP	15	25.0%
RALP	28	46.7%
LRN	5	8.3%
LPN	11	18.3%
RPN	1	1.7%
<b>Marital status</b>		
Married	32	53.3%
Common-law partner	18	30.0%
Single	7	11.7%
Divorced	1	1.7%
Widowed	2	3.3%
<b>Educational attainment</b>		
Primary	3	5.0%
High school	20	33.3%
College	9	15.0%
University	17	28.3%
Professional diploma	10	16.7%
Other	1	1.7%
<b>Annual income</b>		
0–30K	5	8.3%
30–50K	23	38.3%
50–80K	13	21.7%
80–100K	6	10.0%

>100K	9	15.0%
Undeclared	4	6.7%
Ethnicity		
Caucasian	50	83.3%
First Nations	1	1.7%
Metis	1	1.7%
Other	6	10.0%
Undeclared	2	3.3%

LPN: laparoscopic partial nephrectomy; LRN: laparoscopic radical nephrectomy; RALP: robot-assisted laparoscopic radical prostatectomy; RP: radical prostatectomy; RPN: robotic partial nephrectomy

Opioid	n	%
Hydromorphone	53	88.3%
Morphine	2	3.3%
No opioid	4	6.7%
Dose prescribed (n=54)		
Mean	65	55.1; 74.9 (95% IC)
Median	55	50.0; 100.0 (Q1; Q3)
Total	3510	
Dose used (n=55)		
Mean	30.0	17.8; 42.2 (95% IC)
Median	15.0	0.0; 40.0 (Q1; Q3)
Dose unused (n=55)		
Mean	40.4	30.5; 50.2 (95%IC)
Median	35.0	0.0; 75.0 (Q1; Q3)
Total	2220	

Co-analgesia		
Acetaminophen	49	89.1
Naproxen	3	5.5
Ibuprofen	1	1.8
Pregabalin	1	1.8
Oxybutinin	2	3.6

**Table 3. Patient-reported management of unused opioids**

Unused opioids management	1 month		3 months	
	n	%	n	%
Returned to pharmacy	8	13.3	12	20.0
Kept at home	30	50.0	29	48.3
Disposed	2	3.3	0	0.0
No unused opioids	6	10.0	9	15.0
Prescription not fulfilled	6	10.0	0	0.0
Given to someone	0	0.0	1	1.7
Used for other reason	0	0.0	1	1.7
Other	0	0.0	3	5.0
No detail	8	13.3	5	8.3