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TOPIC PAPER

Tips and tricks in achieving zero peri-operative opioid used in onco-urologic surgery

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Abstract

Purpose To review non-opioid based protocols in urologic oncologic surgery and describe our institutional methods of eliminating peri-operative opioids.

Methods A thorough literature review was performed using PUBMED to identify articles pertaining to reducing or eliminating narcotic use in genitourinary cancer surgery. Studies were analyzed pertaining to protocols utilized in genitourinary cancer surgery, major abdominal and/or pelvic non-urologic surgery.

Results Reducing or eliminating peri-operative narcotics should begin with an institutionalized protocol made in conjunction with the anesthesia department. Pre-operative regimens should consist of appropriate counseling, gabapentin, and acetaminophen with or without a non-steroidal anti-inflammatory medications. Prior to incision, a regional block or local anesthetic should be delivered. Anesthesiologists may develop opioid-free protocols for achieving and maintaining general anesthesia. Post-operatively, patients should be on a scheduled regimen of ketorolac, gabapentin, and acetaminophen.

Conclusion Eliminating peri-operative narcotic use is feasible for major genitourinary oncologic surgery. Patients not only have improved peri-operative outcomes but also are at significantly reduced risk of developing long-term opioid use. Through the implementation of a non-opioid protocol, urologists are able to best serve their patients while positively contributing to reducing the opioid epidemic.

Keywords Non-opioid · Opioid crisis · Pain management · Urologic oncology

Introduction

The opioid crisis has reached critical new levels in the United States with prescriptions for narcotics increasing 150% in 10 years [1]. While several factors influence this societal epidemic, at least one-third of new opioid users get their first narcotic prescription from surgeons post-operatively. Further, surgeons will often over prescribe narcotics post-operatively while also not informing patients how to dispose of the unused medication properly [2]. In fact, at least 67% of patients have unused opioids in their homes, and less than 10% of patients dispose of extra medication in an FDA-recommended manner [3].

Urologists are no exception to this trend, particularly those performing major oncologic surgeries. One study found that after major kidney or prostate surgery, 60% of opioids were unused for both open and minimally invasive techniques. Interestingly, the prescribing patterns were associated with the physician's personal practices rather than surgery type. In this study, 155 patients accounted for an excess of 2622 narcotic pills in the community [4]. While over prescribing and improper disposal is certainly an ongoing issue, the act of introducing a patient to narcotics is unto itself adding to the opioid epidemic. Indeed, among patients whose first narcotic use was limited to one day, 6% remained on opioids at one year. This number increased to 13.5% if opioids were continued for eight or more days [5].

Furthermore, narcotics have been associated with negatively impacting patients recovery. They have detrimental effects on the bowel leading to ileus and constipation and on the CNS causing dizziness, and in some cases, altered

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mental status and respiratory depression. Narcotics can also contribute to post-operative nausea and vomiting and contribute to urinary retention. These negative side effects have been shown to increase hospital length of stay [6].

Urologists, among many other surgical specialties, are beginning to develop enhanced recovery pathways after surgery (ERAS) protocols including, but not limited to, non-narcotic protocols to help improve post-operative outcomes as well as do their part in helping decrease the number of narcotic prescriptions. In this paper, we aim to review non-opioid protocols in uro-oncologic surgeries divided into the pre-, intra-, and post-operative period. We also aim to discuss the experience at our own institution, and tips to achieving zero opioid use peri-operatively in the oncologic setting.

Literature review/methods

Our literature search was conducted on PubMed and Google Scholar to identify relevant literature regarding the use of non-opioid, or reduced opioid pain medications usage for urologic oncologic surgeries. Our search terms, number of articles found, and number of articles included can be found in Table 1. Published randomized control trials, reviews, other relevant retrospective and prospective studies, and abstracts both published or presented at conferences deemed relevant were used in this review paper. Our search only included articles written in the English language. Cited references from the relevant studies were also assessed for potential inclusion. Articles that focused on non-oncologic aspects of adult urology, such as articles pertaining to pediatric urology, endourology, reconstructive urology were not used in the discussion of this paper. We did include literature from other surgical fields, particularly colorectal and gynecologic, that focused on eliminating or reducing narcotics for major abdominal or pelvic surgery. We did not have a time limit on our search results, as we aimed to include all relevant, published literature. The search was performed in March 2020 using the above search criteria. Three authors (ABK, BME, JLP) independently performed the literature search. After careful review, articles deemed most relevant were used for the focus in this specific review paper. A summary of the articles selected can be found in Table 2.

Results

Pre-operative

Achieving zero narcotics begins pre-operatively. While evidence remains anecdotal, counseling of the patient by the surgeon and surgical team is crucial to manage expectations of postoperative pain. This discussion should include the importance of incorporating non-opiate medication [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen] and also non-medication alternatives, such as meditation or massage [7]. In our practice, post-operative compliance by the patients is most successful when adequate time is used to educate the patient on the contributions narcotics have on recovery and set expectations regarding pain.

Pre-emptive analgesia has emerged as an important component of post-operative pain control. Post-operative pain is thought to be heightened by noxious stimuli during surgery from the periphery to the spinal cord. As such, the most promising early studies came from a combination of intravenous NSAID, reducing the inflammation response, as well as infiltration of the skin with a local anesthetic prior to incision, which should diminish the barrage of C-fiber activation [8].

Further, post-operative ileus (POI) and opioid-induced constipation (OIC) have similar multifactorial pathways. These include surgical stress and the associated inflammatory response with bowel manipulation, as well as opioids used intra-operatively to induce and maintain anesthesia [9–11] Giving the peripherally acting mu-opioid antagonist, alvimopan, has been shown in a placebo-controlled RCT

Table 1 Literature search strategy

Keywords	Boolian operators	# of unique results	# of studies included
P—urologic Oncology I—no opioid/narcotic	"Urologic Oncology" AND no opioid* OR narcotic*	18	4
P—prostatectomy I—no opioid/narcotic	"Prostatectomy" AND no opioid OR narcotic*	241	5
P—cystectomy I—no opioid/narcotic	"Cystectomy" AND no opioid OR narcotic*	74	3
P—nephrectomy I—no opioid/narcotic	"Nephrectomy" OR "Partial nephrectomy" AND no opioid* OR narcotic	253	1

Studies included only once if overlapping categories

P patient/population, *I* intervention

Table 2 Summary of studies included

References	Study design	Sample size	Surgery performed	Intervention	Outcome
Theisen et al. [4]	Review	N/A	RARP	Evaluation of the literature on the use of non-opioid protocols for radical prostatectomy	Sufficient evidence exists to support non-opioid pathways for prostatectomy
Lee et al. [12]	RCT	Alvimopan ($n=143$) Placebo ($n=137$)	Cystectomy (open or RARC)	Oral alvimopan 12 mg versus placebo to assess time to diet and time to bowel function	Alvimopan cohort experienced quicker GI-2 recovery (5.5 vs. 6.8 days; hazard ratio: 1.8; $p<0.0001$), shorter mean LOS (7.4 vs. 10.1 days; $p=0.0051$), and fewer episodes of POI-related morbidity (8.4% vs. 29.1%; $p<0.001$)
Hah et al. [13]	RCT	Gabapentin ($n=208$) Placebo ($n=202$)	Multiple	Gabapentin, 1200 mg, preoperatively and 600 mg, 3 times a day postoperatively or active placebo (lorazepam, 0.5 mg) preoperatively followed by inactive placebo postoperatively for 72 h and time to pain resolution/opioid cessation	No effect on time to pain cessation 24% increase in the rate of opioid cessation after surgery (HR 1.24; 95% CI 1.00–1.54; $p=0.05$) in gabapentin group
Ozmete et al. [14]	RCT	Paracetamol ($n=30$) Placebo ($n=30$)	Cesarean section	1 g paracetamol vs. placebo (NaCl) 15 min prior to incision and assessing pain and narcotic use post operatively	Pre-operative paracetamol significantly reduces post-operative pain and morphine consumption
Talwar et al. [15]	Prospective cohort	RARP ($n=87$), RARN ($n=25$), RAPN ($n=58$)	RARP, RARN, RAPN	Implementation of a standardized non-opioid protocol versus traditional pain management and assessment of pain control	67.7% of patients were discharged without the need for any opioids post-operatively
Audenet et al. [16]	Prospective cohort	Non-opioid ($n=52$) Opioid ($n=48$)	RARC	Feasibility of non-opioid pathway for RARC with ECUD	Non-opioid protocol median time to regular diet was significantly shorter (4 days [IQR 3–5] vs. 5 days [IQR 4–8], $p=0.002$) and the length of stay was 2 days shorter compared to the control group (5 days [IQR 4–7] vs. 7 days [IQR 6–11], $p<0.001$). Direct costs within 30 days after initial surgery, the non-opioid protocol was associated with an 8.6% reduction as compared to the control group ($p=0.032$)

Table 2 (continued)

References	Study design	Sample size	Surgery performed	Intervention	Outcome
Trabulsi et al. [17]	Prospective cohort	Non-opioid ($n=30$) Opioid ($n=30$)	RARP	Non-opioid: pregabalin 150 mg, acetaminophen 975 mg, and celecoxib 400 mg orally 2 h before the start of the procedure and continued postoperatively vs. opioid: intravenous ketorolac 15 mg every 6 h with oxycodone 5 mg and acetaminophen 325 mg, 1–2 tablets, every 4 h as needed	Non-opioid group had significantly less intraoperative opioid requirement (MME 38.4 mg vs. 49.1 mg, $p<0.01$), and significantly less postoperative opioids (MME 49.1 mg vs. 75.3 mg, $p<0.001$)
Yu et al. [18]	Meta-analysis	TAP block ($n=96$) Local ($n=100$)	Multiple lower abdominal	Transversus abdominis-plane block versus local anesthetic wound infiltration	No significant difference between groups in 24-h post-operative morphine requirements
Pedrazzani et al. [19]	Prospective cohort	TAP block + local ($n=24$) Local ($n=24$)	Elective laparoscopic colorectal resection	TAP block and local wound infiltration versus local alone with an ERAS protocol	No significant difference in overall pain. However, there was a significant difference in fewer post-operative opioids for TAP + local vs. local alone ($p=0.0009$)
Huang et al. [20]	RCT	QL block ($n=38$) TAP block ($n=39$)	Elective laparoscopic colorectal resection	QL block vs. TAP block and cumulative morphine consumption postoperatively	Morphine consumption 24 h postoperatively was significantly lower in the QL group than in the TAP group (estimated median difference − 8 mg, adjusted 95% confidential interval − 12 to − 6 mg, $p<0.001$)
Cacciamani et al. [21]	RCT	TAP block + local ($n=57$) Local ($n=43$)	RARP	TAP block + local vs. local and postoperative pain and opioid demand during a hospital stay	TAP block group showed a decreased mean Numerical Rating Scale (NRS) within 12 h after surgery (1.6 vs. 2.6; $p=0.02$) and mean NRS (1.8 vs. 2.7; $p=0.04$) with lesser number of patients who used opioid (3.5% vs. 18.6%; $p=0.01$)
Skjelsager et al. [22]	RCT	TAP block ($n=23$) Local ($n=25$) Placebo ($n=25$)	Open prostatectomy	TAP block vs. local (placebo controlled) in the setting of preoperative gabapentin, ibuprofen, and paracetamol and post-operative morphine	Neither TAP block nor local anesthesia outperformed placebo for post-operative pain score or morphine consumption
Greenberg et al. [23]	Prospective cohort	Reduced opioid ($n=54$) Standard ($n=50$)	Cystectomy (open or RARC)	Implementation of a reduced opioid protocol for radical cystectomy and pain scores, LOS, complications, readmission, and mortality	No significant difference in pain scores, LOS, complications, readmissions, or mortality 77% reduction in opioids in reduced opioid pathway

RARC robotic-assisted radical cystectomy, *RARP* robotic-assisted radical prostatectomy, *RARN* robotic-assisted radical nephrectomy, *RAPN* robotic-assisted partial nephrectomy, *LOS* length of stay, *ECUD* extracorporeal urinary diversion, *MME* mean morphine equivalents, *TAP* transversus abdominis plane, *QL* quadratus lumborum

to reduce POI and increase gastrointestinal recovery when given pre-operatively. Oral alvimopan 12 mg was given pre-operatively and continued post-operatively while patients recovered. The treatment group had a significantly quicker GI recovery, shorter length of stay, and fewer episodes of POI-related morbidity compared to the placebo group [12]. This study clearly shows the contribution of opioids in genitourinary cancer, radical cystectomy, in post-operative morbidity.

Two randomized clinical trials (RCT) have evaluated the use of pre-medication with gabapentin or acetaminophen (paracetamol) on post-operative pain management. Though these studies were not urology specific, both included major abdominal and/or pelvic surgery. The first study randomized patients to gabapentin versus placebo. Patients in the treatment arm received 1200 mg of gabapentin pre-operatively, and then 600 mg three times per day for a total of ten doses (72 h). While there was no difference in time to pain cessation, peri-operative gabapentin had a 37% increase in opioid cessation after surgery, as well as a 7 day decrease in the amount of time taking opioids post-operatively [13].

A second study randomized women undergoing cesarean section to 1 g paracetamol 15 min prior to induction of anesthesia versus placebo. All patients received morphine patient-controlled analgesia (PCA). Patients in the treatment arm, after a single dose of paracetamol, had significantly less post-operative pain and used less total morphine over a 24-h period [14].

Urologists have implemented variations of the studied regimens. Pre-emptive pain control for major urologic oncologic surgery typically consists of one dose of gabapentin, 300 mg to 600 mg, and acetaminophen, which is given either orally 1 h prior to surgery or intravenously 15 min prior to surgery. Some protocols include the use of an NSAID, such as celecoxib 600 mg, in addition [15–17]. Regardless of the protocol used, the goal of pre-operative pain control should be targeted to diminish noxious stimuli to the CNS intraoperatively, initiate pain control with non-opioid medications, and proper counseling to set patient expectations.

Intra-operative

With respect to intra-operative analgesia, many groups have adopted a multimodal approach with the use of multiple drug classes to ensure patients have optimal pain control with minimal side effects from any single medication. Common considerations when it comes to intra-operative analgesia in genitourinary oncologic procedures include the use of transversus abdominis plane (TAP) blocks, quadratus lumborum (QL) blocks, and/or local wound anesthetic.

Much of the intra-operative non-narcotic data has been extrapolated from colorectal surgery. One metanalysis performed among multiple surgery types compared the efficacy of TAP block versus local wound infiltration and found similar immediate post-operative pain reporting, but patients receiving TAP block had reduced pain for a longer interval of time compared to those with local alone [18]. Further, another study reported that patients undergoing laparoscopic colorectal surgery receiving both TAP block and local wound infiltration used significantly fewer opioids post-operatively compared to those who received local analgesia alone [19]. Though TAP block appears to be reported more frequently in the literature, a recent RCT compared TAP block to QL block in patients undergoing laparoscopic colorectal surgery. Patients with QL block not only used less morphine than the TAP block group but also reported superior post-operative pain control satisfaction [20].

Intra-operative considerations for reducing opioid use have also been reported for both prostatectomy and nephrectomy surgeries. A recent RCT showed that for patients undergoing robotic-assisted radical prostatectomy (RARP), the combination of local wound anesthetic infiltration with 20 mL of 0.35% ropivacaine and bilateral TAP block with 20 mL of 0.35% ropivacaine improved postoperative pain control, reduced opioid administration (3.5% vs. 18.6%; $p=0.01$), and led to a shorter hospital stay (4.27 vs. 4.72 days; $p=0.04$) than local wound anesthetic alone [21]. Likewise, the PENN Initiative is a standardized non-opioid analgesia pathway which includes 30 cc of 0.5% bupivacaine in all robotic port sites before incision. This protocol was prospectively used in 170 patients undergoing either RARP ($n=87$), robotic-assisted radical nephrectomy (RARN) ($n=25$), or robotic-assisted partial nephrectomy (RAPN) ($n=58$) and showed a reduction in the percentage of patients who were discharged with opioids from 100 to 32.3%, with no difference in pain scores [15].

However, for patients undergoing open radical retropubic prostatectomy, the data has been less robust. One study showed no added benefit in pain scores or morphine consumption with either intra-operative bilateral TAP blocks with 20 mL ropivacaine or wound infiltration with 40 mL ropivacaine 0.75% when compared to placebo [22].

The use of blocks is important to minimize the use and prescription of narcotics post-operatively as well as intra-operatively. This is of utmost importance to help reduce the opioid epidemic. Also of importance is the need to reduce narcotic use to help with patient recovery. In urologic oncology, this is particularly true for radical cystectomy. It is extremely important that the surgeons and anesthesiologist work as a team, given that narcotics are used as part of the general anesthetic regimen. Our work recently showed the implementation of a non-opioid protocol for 52 patients undergoing robot-assisted radical cystectomy (RARC) with extracorporeal urinary diversion. Working with our anesthesia colleagues, they identified an intra-operative protocol without narcotics consisting of general anesthesia induction

with ketamine 0.5 mg/kg and propofol 1.5 to 2.5 mg/kg, dexmedetomidine (0.4 mcg/kg/h after a bolus of 1 mcg/kg over 20 min), and regional TAP or QL blocks with 30 mL of 0.25% bupivacaine. Intra-operative analgesic medication included IV acetaminophen every 6 h from pre-operative oral dose and ketorolac 30 mg at the end of the procedure [16]. This protocol was shown to be effective and safe. Additionally, Greenberg et al. reported on the implementation of a reduced opioid utilization protocol for radical cystectomy patients, but the only mention of an intra-operative protocol was that surgeons were encouraged to utilize local anesthetic agents including bupivacaine administered in multiple layers of the lower midline incision [23].

Post-operative

Post-operative pain control in open, laparoscopic, and robotic genitourinary cancer surgery is arguably the most difficult time to achieve a non-narcotic pain pathway. Although complete non-opioid post-operative pathways in urologic oncologic surgery are relatively uncommon, there have been more attempts at attaining this goal with the additional negative side effects of these drugs in the post-operative setting, primarily with delaying return in bowel function. The newer non-narcotic literature shows that many of the medications and pathways being used post-operatively amongst various urology centers are very similar, utilizing multimodal non-opioid medications after surgery with slight variations in dosing, frequency, and duration without optimal protocols well established.

The PENN study used an already established "PENN Initiative Non-Narcotic Pathway" for pain management protocols. Post-procedurally, patients received 300 mg of gabapentin every 8 h and 975 mg of oral acetaminophen every 8 h. Patients also received 15 mg of ketorolac every 6 h during postoperative day (POD) 1. If these patients were also found to have < 500 cc of blood loss intraoperatively, a normal functioning contralateral kidney in the case of a partial or radical nephrectomy, and a baseline creatinine of < 1.4 mg/days, then patients also were eligible to receive 600 mg of ibuprofen every 6 h for the following postoperative days. In the setting of uncontrolled pain, patients were escalated to tramadol 50 mg or 100 mg every 6 h, based on pain scores, and then oxycodone 5 mg or 10 mg if the pain scores were still elevated with tramadol. All patients were sent home with acetaminophen, ibuprofen, and gabapentin, with an additional 10 pills of tramadol or oxycodone only if they required such medications post-operatively. Their data shows 67.7% of patients were sent home without any narcotics and only 8.2% of patients were sent home with oxycodone. As an institution, they were able to decrease narcotic prescribing in patients undergoing these three surgeries from 100% to 32.3% [15].

The Michigan Opioid Prescribing and Engagement Network also recently published a study where they offered patients undergoing six different surgeries, one of which being RARP, the option for no narcotics post-operatively, without any changes to the pre- or intra-operative pain medications regularly given for this procedure. Patients were scheduled to stagger taking 600 mg of ibuprofen and 650 mg of acetaminophen every 6 h in the postoperative setting. RARP patients were discharged with an average of six 5 mg oxycodone pills as rescue pain medications if needed. Of the men undergoing RARP, 47% of men did not use any form of post-operative narcotics and only 2% of men in this study requested additional narcotics for sufficient pain control [24].

Similarly, Theisen and Davies suggest using standing IV acetaminophen and IV NSAIDs with an only minimal breakthrough, low dose narcotics. These patients are discharged after prostatectomy with oral acetaminophen and NSAIDs and only a small amount of narcotics if the patient requires it. Currently, preliminary data shows no increase in patient-reported post-operative pain scores between the no narcotic and control groups [7].

There are few papers assessing the feasibility of non-opioid protocols after surgery in patients undergoing radical cystectomy with diversions, likely due to the magnitude and morbidity associated with the procedure. Our group established a zero narcotic pathway for all RARC with extracorporeal urinary diversion. The post-operative pain regimen included 1 g acetaminophen every 6 h, ketorolac 30 mg every 6 h, and gabapentin 100 mg every 8 h. All medications were scheduled with the availability of narcotics only for breakthrough pain. This group, when compared to the standard narcotic group, used significantly less morphine equivalents (2.5 vs. 44) with no significant changes in post-operative pain scores and statistically significant improvement in time to return to a regular diet (4 vs. 5 days). Hospital stay was also significantly shorter (5 vs. 7 days) in the non-opioid group [16]. Furthermore, no patients were sent home with a narcotic prescription and using the Internet System for Tracking Over-Prescription (I-STOP), we identified that only 4 (7.8%) of patients required a prescription within 6 months of discharge.

The Shah research group recently published on their reduced opioid utilization (RUO) protocols for patients undergoing both open and laparoscopic radical cystectomy. The medications used after surgery were similar to the ones mentioned in the aforementioned study, with acetaminophen 1 g every 6 h, ketorolac 15 mg/mL every 6 h, and gabapentin 100 mg every 8 h. Tramadol 50 mg was used for breakthrough pain. This study also mentions the use of other non-medication treatments such as abdominal binders and ice packs to help with patient pain relief. If pain relief was inadequate, patient specific, minimal narcotic medications

Table 3 Sample institutional protocol for eliminating peri-operative narcotic use

Pre-operative	Intra-operative	Post-operative
300–600 mg gabapentin 30–60 min prior to induction 1 g IV acetaminophen 15 min prior to induction ±600 mg celecoxib 30–60 min prior to induction	TAP/QL block and/or Multiplane local analgesia after induction prior to the first incision IV acetaminophen q6 hours after pre-operative dose 15–30 mg ketorolac prior to extubation	1 g IV acetaminophen q6 hours 15–30 mg ketorolac q6 hours 100 mg gabapentin q8 hours

were prescribed along with the gut motility agent alvimopan. This study showed a significant reduction in opioid usage in both post-anesthesia care unit (PACU) and on the floor after cystectomy. 20.4% of patients received zero narcotics in the experimental group compared to 0% of the control group. They demonstrated no significant difference in pain score on POD 1, 2, and 3 between the two groups. There were significant benefits in return of bowel function, time to tolerating a regular diet, and time to ambulate out of bed with the study cohort [23].

Tips and tricks

At our own institution, we have worked closely with the anesthesia and pain department to implement zero opioid protocols for patients undergoing major genitourinary oncologic surgery. Listed below are aspects which have allowed us to create a successful program, as well as a sample zero narcotic protocol based on the literature above (Table 3).

1. Set patient expectations about post-operative pain control with a non-opioid protocol
2. Partner with the anesthesiology and/or pain management department to collaborate on design and implementation
3. Give pre-emptive analgesia with gabapentin and acetaminophen with or without an NSAID
4. Perform a TAP or QL block and instill local analgesia prior to incision
5. "Stay ahead of the pain". Patients should have scheduled ketorolac, gabapentin, and acetaminophen
6. Patients should not be discharged with narcotic pain medication unless it was needed regularly while inpatient.

Conclusion

Surgeons have a responsibility to not only manage pain post-operatively, but also reduce the burden of the national opioid epidemic. Developing procedure-specific protocols is of tantamount importance in developing zero opioid protocols. Pain control should begin pre-operatively, not only with medications such as gabapentin, acetaminophen, and NSAIDs but also with managing patient expectations. Non-opioid medications, including local or regional anesthesia and acetaminophen should be continued throughout the surgery to reduce noxious stimuli transmitted to the CNS. Patients should not wait for post-operative pain to receive analgesia and should have a scheduled regimen. By implementing institutional protocols, reaching zero opioid use is feasible in genitourinary oncologic surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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