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Original Article

Prospective implementation of a nonopioid protocol for patients undergoing robot-assisted radical cystectomy with extracorporeal urinary diversion

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Abstract

Objectives: To evaluate the feasibility and outcomes of a nonopioid (NOP) perioperative pain management protocol for patients undergoing robot-assisted radical cystectomy (RARC).

Materials and Methods: We prospectively included 52 consecutive patients undergoing RARC at our institution for bladder cancer. Patients received a multimodal pain management protocol, including a combination of nonopioid pain medications and regional anesthesia. For comparison, we retrospectively included 41 consecutive patients who received the same procedure before implementation of the NOP protocol.

Results: There was no significant difference in demographic and perioperative characteristics between the two groups. Patients included in the NOP protocol received a much lower dose of postoperative morphine milligram equivalents (2.5 [IQR: 0−23] vs. 44 [14.5−128], $P < 0.001$), with no difference in pain scores. In the NOP protocol, the 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], $P < 0.001$). When evaluating the direct costs within 30 days after initial surgery, the NOP protocol was associated with an 8.6% reduction as compared to the control group ($P = 0.032$). In multivariate analysis, the receipt of the NOP protocol was a significant predictor of a length of stay <7 days after RARC (OR: 12.09; 95% CI: 1.70−140; $P = 0.023$).

Conclusions: The prospective implementation of a NOP protocol for patients undergoing RARC is feasible, allowing for minimal narcotic usage and provides benefits to patients, institutions, and population.

Keywords: Length of stay; Opioid crisis; Pain management; Regional anesthesia; Robot-assisted radical cystectomy

1. Introduction

Bladder cancer represents the fifth most common cancer in the United States, with an estimated incidence of 81,190 new cases in 2018 [1]. Radical cystectomy (RC) is recommended for patients with localized muscle-invasive bladder cancer (MIBC) as well as very high risk nonmuscle invasive bladder cancer [2]. Each year, approximately 6,200 cystectomies are performed in the United States for bladder cancer [3]. This treatment carries a high morbidity, with early complications seen in up to 60% of patients [4], as well as a perioperative mortality rate of approximately 5% [5].

Narcotic-based analgesia has been an integral component of postoperative pain control in all major surgical interventions, including RC, with negative effects on bowel movements and potential risk of addiction. In recent years, the opioid epidemic has reached crisis proportions in the United

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States and has been a major contributor to the 64,000 American deaths due to drug overdose in 2016, which represents a 21% increase from 2015 [6]. Drug overdoses have become the leading cause of death in Americans less than 50 years old, and the use of opioid pain relievers accounts for approximately half of opioid-overdose deaths [7].

With the aim to improve surgical outcomes and patients' recovery, robot-assisted radical cystectomy (RARC) has gained increased utilization in the United States [8]. However, patients remain exposed to the potentially adverse effects of narcotic use. In this study, we described the feasibility and outcomes of the prospective implementation of a nonopioid (NOP) protocol for patients undergoing RARC.

2. Material and methods

2.1. Study population

Within the context of an Institutional Review Board-approved protocol, we prospectively included all consecutive patients who underwent RARC for MIBC or high-risk NMIBC at our institution, after implementation of a nonopioid perioperative protocol, from November 1st, 2016 to December 31st, 2017. Radical cystectomy and extended lymph node dissection were performed robotically by two surgeons (KB and JPS) as previously described [9]. Urinary diversion was created through the extraction incision, but urinary anastomoses were performed intracorporeally. For comparison purpose, we retrospectively included consecutive patients who received the same procedure at our institution by the same surgeons, before implementation of the NOP protocol, from October 1st, 2016 to October 31st, 2017. No formal enhanced recovery after surgery (ERAS) pathway was implemented in our department, although most of its principles were followed in daily practice, including absence of bowel preparation, nasogastric tube removed after surgery, oral fluids started the evening of surgery, and early mobilization. No patient received alvimopan.

2.2. Nonopioid (NOP) protocol

Patients received acetaminophen 1000 mg, gabapentin 600 mg, and celecoxib 600 mg per os immediately preoperatively. General anesthesia was induced using ketamine 0.5 mg/kg and propofol 1.5 to 2.5 mg/kg, but no fentanyl. During surgery, patients received propofol 75 to 125 mcg/kg/min, ketamine 5 to 10 mcg/kg/min to a total dose of 150 mg and dexmedetomidine 0.4 mcg/kg/h after a bolus of 1 mcg/kg over 20 minutes. Regional block was systematically associated under sedation before surgery, with quadratus lumborum (QL) block or transversus abdominis plane (TAP)/rectus sheath block, using 30 ml of 0.25% bupivacaine by side, as previously described [10]. Intraoperative analgesic medications included acetaminophen IV every 6 hours from preoperative oral dose and ketorolac 30 mg at the end of the procedure. Postoperative pain was managed with intravenous acetaminophen 1000 mg IV, ketorolac 30 mg IV every 6 hours and gabapentin 100 mg every 8 hours. In patients with renal insufficiency the ketorolac was held. In case of severe refractory pain, intravenous hydromorphone could be prescribed as needed but no patient-controlled analgesia (PCA). Before the NOP protocol implementation, pain management was not standardized, and pain control was achieved without regional block, with a combination of opioid PCA and IV narcotics based on an as needed basis.

2.3. Data collection

Patient information, including sex, age, race, body mass index, American Society of Anesthesiologists score, Charlson comorbidity index, smoking status, clinical state at surgery, and receipt of neoadjuvant chemotherapy was collected. Pertinent operative details such as operative duration, estimated blood loss, transfusion, urinary diversion (ileal conduit or neobladder) were also collected. Pain score was calculated for each patient as the mean of the pain scores reported in the nurses' notes on every shift. Length of stay, time to liquid diet, time to regular diet were also collected. All complications within 30 days were reported using the Clavien–Dindo classification [11]. Narcotic requirements were aggregated for each patient and converted to oral morphine equivalents using standard opioid conversions. Direct healthcare costs were supplied by the financial department of our institution and compared between groups for resources, hospital stay, and readmissions within 30 days after initial surgery.

2.4. Statistical analysis

The two groups, NOP protocol and control group, were compared in intention-to-treat. We used Chi-squared and Fisher exact tests to analyze differences between clinical and demographic categorical variables, and Wilcoxon and Kruskal–Wallis tests for continuous variables comparison. Multivariable logistic regression was utilized to identify perioperative characteristics associated with a length of stay shorter than 7 days after RARC. A P value < 0.05 was considered statistically significant. For reasons of confidentiality, direct costs were not presented as absolute values but percentage differences between the two groups. All analyses were conducted using R v.3.5 (https://cran.r-project.org).

3. Results

In total, we prospectively included 52 patients who underwent RARC within the NOP protocol and compared them to a control group of 41 patients. Demographic characteristics are presented in Table 1. There was no significant difference in age, gender, race, median body mass index, median American Society of Anesthesiologists score, median Charlson comorbidity index, or smoking status between the two groups. Overall, 67% of the patients

presented with MIBC and 30% received neoadjuvant chemotherapy, with no difference between the groups. The proportion of neobladder was higher in the NOP protocol (21% vs. 5%) without reaching significance ($P = 0.052$). The median time of surgery was 325 minutes [interquartile range (IQR): 292−391] in the NOP group vs. 367 min [IQR: 292−391] ($P = 0.065$). There was no difference in the median estimated blood loss (200 ml in both groups). The transfusion rate was lower in the NOP group (19.2% vs. 28.2% in the control group) without reaching significance ($P = 0.451$).

Patients included in the NOP protocol effectively received a much lower dose of morphine milligram equivalents during their stay at hospital (2.5 [IQR: 0−23] vs. 44 [14.5−128], $P < 0.001$), with no difference in pain scores (Table 2). In the NOP protocol, the first five patients received TAP block and all the following patients routinely got QL block, after it was shown to be more effective [12]. Overall, 31 patients (60%) did not receive any opioid at all during their postoperative course. The median time to regular diet was significantly shorter in the NOP protocol (4 days [IQR: 3−5] vs. 5 days [IQR: 4−8], $P = 0.002$). The length of stay was 2 days shorter in the NOP protocol compared to the control group (5 days [IQR: 4−7] vs. 7 days [IQR: 6−11], $P < 0.001$) (Fig. 1). Furthermore, using the Internet System for Tracking Over-Prescription, we identified only four patients (8%) in the NOP group who had narcotic prescription within 30 days after discharge. Overall, the complication rate within 30 days was 52%, with 34% of grade ≥3 according to Clavien−Dindo classification. No significant difference was found between the two groups. However, the rate of ileus, defined as repeated vomiting with epigastric dysfunction or in the presence of small bowel obstruction, was lower in the NOP protocol (13% vs. 29%), although it didn't reach significance ($P = 0.106$). When evaluating the direct costs within 30 days after initial surgery, the NOP protocol was associated with an 8.6% reduction as compared to the control group ($P = 0.032$).

In multivariate analysis, after adjusting for all potential clinical confounders, the receipt of the NOP protocol was a significant predictor of the length of stay <7 days after RARC (OR: 12.09; 95% CI: 1.70−140; $P = 0.023$), while increased perioperative blood loss and postoperative ileus were significantly associated with a length of stay ≥7 days (OR: 0.99; 95% CI: 0.98−1; $P = 0.034$ and OR: 0.02; 95% CI: 0.01−0.15; $P = 0.003$) (Table 3).

4. Discussion

Radical cystectomy is a major surgery, associated with high pain levels. Administration of morphine by PCA has extensively improved the management of postoperative pain [13]. However, it has some limitations, including moderate efficacy on relieving pain during movement and side-effects on bowel movements such as nausea and vomiting, which could delay postoperative rehabilitation. Furthermore, the soaring death rate from opioid overdose prompted the President of the United States to declare the country's opioid epidemic a "national public health emergency" in 2017. It is noteworthy that half of opioid-overdose deaths are related to the use of opioid pain relievers, while the

Table 1
Characteristics of the study population.

Variables	All patients N = 93	Control N = 41	No NARC N = 52	*P* value
Gender:				0.243
Male	68 (73.1%)	27 (65.9%)	41 (78.8%)	
Female	25 (26.9%)	14 (34.1%)	11 (21.2%)	
Median age at surgery, years [IQR]	71.0 [62.3; 77.5]	71.0 [67.0; 77.0]	69.7 [60.9; 77.5]	0.642
Race:				0.553
White	66 (71.0%)	30 (73.2%)	36 (69.2%)	
African-American	14 (15.1%)	7 (17.1%)	7 (13.5%)	
Other	13 (14.0%)	4 (9.76%)	9 (17.3%)	
Median BMI, kg/m^2 [IQR]	25.9 [23.4; 29.4]	24.6 [22.6; 29.1]	27.5 [24.3; 29.8]	0.114
Median ASA score [IQR]	3.00 [2.00; 3.00]	3.00[2.00; 3.00]	3.00 [3.00; 3.00]	0.817
Median CCI [IQR]	6.00 [5.00; 9.00]	6.00 [5.00; 9.00]	6.50 [5.00; 8.75]	0.882
Smoking status:				0.998
Never	17 (18.3%)	8 (19.5%)	9 (17.3%)	
Current - Former	76 (81.7%)	33 (80.5%)	43 (82.7%)	
Clinical state at cystectomy:				0.441
MIBC	63 (67.7%)	30 (73.2%)	33 (63.5%)	
NMIBC	30 (32.3%)	11 (26.8%)	19 (36.5%)	
Neoadjuvant chemotherapy:				0.701
No	65 (69.9%)	30 (73.2%)	35 (67.3%)	
Yes	28 (30.1%)	11 (26.8%)	17 (32.7%)	

ASA = American Society of Anesthesiologists; BMI = body mass index; CCI = Charlson comorbidity index; IQR = interquartile range.

Table 2
Comparison of perioperative outcomes between the 2 groups (*P* values in bold are statistically significant).

Variables	All patients N = 93	Control N = 41	No NARC N = 52	*P* value
Type of diversion:				0.052
Ileal conduit	80 (86.0%)	39 (95.1%)	41 (78.8%)	
Neobladder	13 (14%)	2 (4.88%)	11 (21.2%)	
Median operative duration, min [IQR]	342 [299; 424]	367 [318; 438]	325 [292; 391]	0.065
Median estimated blood loss, ml [IQR]	200 [150; 300]	200 [150; 300]	200 [100; 300]	0.236
Transfusion:				0.451
No	70 (76.9%)	28 (71.8%)	42 (80.8%)	
Yes	21 (23.1%)	11 (28.2%)	10 (19.2%)	
pT stage:				0.443
≤pT1	37 (39.8%)	13 (31.7%)	24 (46.2%)	
pT2	15 (16.1%)	7 (17.1%)	8 (15.4%)	
pT3	25 (26.9%)	14 (34.1%)	11 (21.2%)	
pT4	16 (17.2%)	7 (17.1%)	9 (17.3%)	
pN stage:				0.568
pN0	68 (73.9%)	32 (78.0%)	36 (70.6%)	
pN+	24 (26.1%)	9 (22.0%)	15 (29.4%)	
Time to liquid diet, days [IQR]	2.00 [2.00; 3.00]	2.00 [2.00; 4.00]	2.00 [2.00; 3.00]	0.289
Time to regular diet, days [IQR]	4.00 [3.00; 6.00]	5.00 [4.00; 8.00]	4.00 [3.00; 5.00]	**0.002**
Median pain score [IQR]	1.70 [0.28; 3.30]	1.97 [0.56; 3.82]	1.10 [0.00; 3.00]	0.097
Median postoperative morphine (MME)	15.0 [0.00; 73.5]	44.0 [14.5; 128]	2.50 [0.00; 23.0]	**<0.001**
Length of stay, days [IQR]	6.00 [5.00;10.0]	7.00 [6.00; 11.0]	5.00 [4.00; 7.00]	**<0.001**
Readmission within 30 days:				0.759
No	77 (82.8%)	35 (85.4%)	42 (80.8%)	
Yes	16 (17.2%)	6 (14.6%)	10 (19.2%)	
Complication within 30 days:				0.887
No	45 (48.4%)	19 (46.3%)	26 (50.0%)	
Yes	48 (51.6%)	22 (53.7%)	26 (50.0%)	
Clavien-Dindo grade:				0.222
1-2	29 (63.0%)	12 (52.2%)	17 (73.9%)	
≥3	17 (37.0%)	11 (47.8%)	6 (26.1%)	
Ileus:				0.106
No	74 (79.6%)	29 (70.7%)	45 (86.5%)	
Yes	19 (20.4%)	12 (29.3%)	7 (13.5%)	

IQR = interquartile range; MME = morphine milligram equivalent.

other half falls on illicit use of synthetic opioids [6]. Indeed, up to 13% of patients initiate chronic opioid use after surgery [14]. To address this public health crisis, various policies have been enacted to try and limit opioid pain relievers prescription and promote access to naloxone [7]. Consequently, perioperative teams are facing the challenge to optimally manage pain while reducing prescription of opioids.

Many trials have compared the effects of nonopioid analgesia in combination with morphine on postoperative pain, nausea and vomiting [15]. However, to our knowledge, this study represents the first prospective evaluation of a nonopioid protocol in the setting of radical cystectomy. We found that perioperative anesthesia and perioperative pain management could be achieved without any narcotic in patients undergoing RARC, validating its feasibility. Furthermore, compared to a control group, patients who underwent RARC within the NOP protocol demonstrated a significant improvement regarding time to regular diet, and was associated with a 2-day reduction in the length of stay at hospital. Medico-economic evaluation also found a significant 8.6% reduction in direct costs within the 30-days after initial surgery. To achieve this goal, several approaches need to be combined.

One approach is the concomitant use of nonopioid pain relievers. Balanced analgesia is based on a combination of different drugs to reduce pain while decreasing the postoperative use of morphine [16]. A randomized, double-blind, placebo-controlled trial including 202 patients undergoing thoracic, orthopedic or gynecologic surgery at a single center, demonstrated that perioperative gabapentin alone had a modest effect on promoting opioid cessation after surgery [17]. However, in a recent systematic review and meta-analysis of randomized trials using analgesics other than morphine, including 135 trials with a total of 13,287 patients, the authors found that morphine reduction was the greatest with the combination of two different drugs [15]. Although none of the studies included focused specifically on radical cystectomy, several procedures were pelvic surgery. In a retrospective study, a combination of ibuprofen

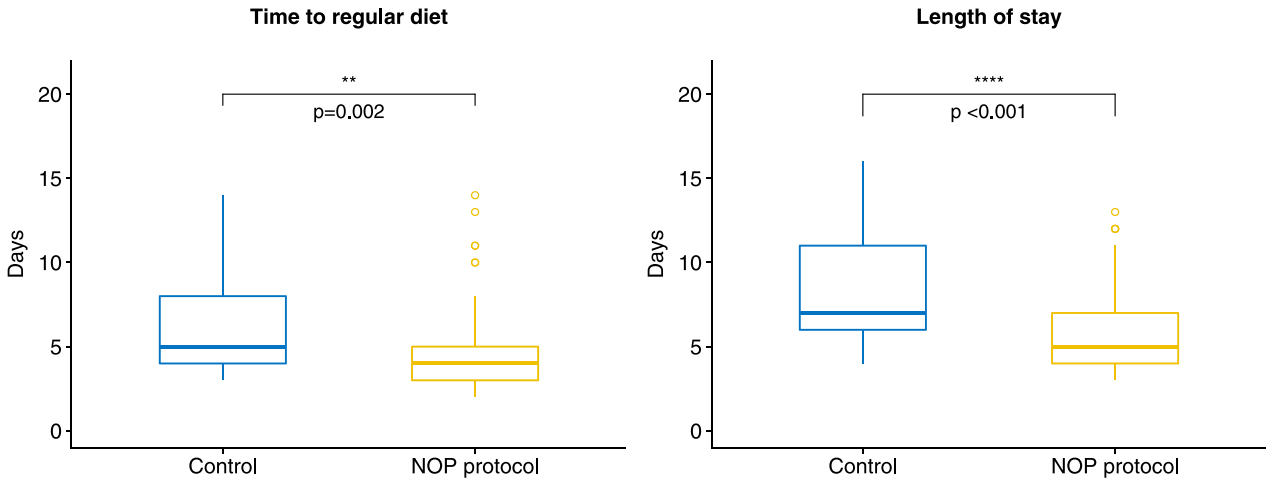

Fig. 1. Box-plot comparing the time to regular diet and the length of stay at hospital between patients undergoing robot-assisted radical cystectomy within the nonopioid (NOP) protocol vs. control.

Table 3
Multivariate logistic regression predicting a length of stay shorter than 7 days after robot-assisted radical cystectomy (*P* values in bold are statistically significant).

Variables	OR [95% CI]	*P* value
Group:		
Control	1.00 (Reference)	
Non-narcotic protocol	12.09 [1.70; 140.27]	**0.023**
Gender:		
Male	1.00 (Reference)	
Female	3.84 [0.67; 28.03]	0.146
Age at surgery (Continuous)	1.03 [0.93; 1.16]	0.599
Race:		
White	1.00 (Reference)	
African-American	1.73 [0.15; 18.82]	0.649
Other	0.51 [0.03; 9.86]	0.646
BMI (Continuous)	1.07 [0.88; 1.34]	0.530
ASA (Continuous)	0.47 [0.11; 1.79]	0.276
CCI (Continuous)	1.03 [0.71; 1.50]	0.882
Smoking status:		
Never	1.00 (Reference)	
Current - Former	0.69 [0.08; 5.76]	0.732
Clinical state at cystectomy:		
MIBC	1.00 (Reference)	
NMIBC	0.57 [0.08; 3.95]	0.556
Neoadjuvant chemotherapy:		
No	1.00 (Reference)	
Yes	0.64 [0.07; 5.98]	0.688
Type of diversion:		
Ileal conduit	1.00 (Reference)	
Neobladder	0.03 [0.00; 0.90]	0.063
Operative duration (Continuous)	1.01 [1.00; 1.02]	0.260
Estimated blood loss (Continuous)	0.99 [0.98; 1.00]	**0.034**
Transfusion:		
No	1.00 (Reference)	
Yes	8.22 [0.45; 240.36]	0.181
Ileus:		
No	1.00 (Reference)	
Yes	0.02 [0.00; 0.15]	**0.003**

ASA = American association of anesthesiologists; BMI = body mass index; CCI = Charlson comorbidity index.

and acetaminophen analgesia after radical prostatectomy reduced the length of stay by 50% and 30% of the patients required no narcotic analgesia during their admission [18]. In our NOP protocol, we used a combination of acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentin, and perioperative ketamine with similar pain scores compared to the control group.

One of the critical components of the multimodal pain management is the use of regional anesthesia. For major abdominal surgery performed by laparotomy, thoracic epidural has shown a significant benefit compared to PCA [19]. It is associated with a better control of pain related to mobilization, a shorter time to bowel movements, and a reduction in morphine use [20]. However, it is counterbalanced by several side effects and does not shorten the duration of hospital stay [21]. Alternative techniques of regional anesthesia, like TAP and QL blocks, are also available with excellent results. In a study with patients undergoing major open urological surgery including radical cystectomy, 50% of patients with rectus sheath catheters didn't use PCA and length of stay was significantly reduced [22]. Similarly, TAP blocks have been shown to decrease short-term opioid use and improve pain outcomes in both open and laparoscopic abdominal surgery [23, 24]. Recently, a retrospective study of patients undergoing radical cystectomy found that TAP block was associated with lower narcotic usage, and significant improvement in time to flatus, bowel movements, and length of stay compared to traditional pain management [25]. In our NOP protocol, the vast majority of patients routinely got QL block after it was shown to be more effective than TAP block in a randomized controlled trial [12].

Minimally-invasive surgery plays a major role to improve postoperative recovery, including pain reduction. It has been shown to decrease parietal trauma and inflammatory reaction [26]. The maturation of robot-assisted surgery coupled with

proficiency in technique has resulted in increasing uptake and utilization of RARC. In the National Cancer Database, the use of RARC has increased over time from 16.7% in 2010 to 25.3% in 2013 [8]. In the literature, RARC is associated with lower intraoperative blood loss and transfusion rate, shorter time to normal diet and decrease in length of stay, but a higher 30-day cost [27,28]. Although initial publications suggested a possible higher risk of atypical recurrence, a randomized trial demonstrated that RARC was noninferior to open cystectomy for 2-year progression-free survival [29]. Consequently, an approach combining RARC and NOP protocol has the potential to further improve patients' outcomes and to reduce direct cost.

There are a number of limitations in this study. Although patients were prospectively included in the NOP protocol, they were compared to a retrospective cohort of patients undergoing the same surgery, which can introduce temporal selection bias. We didn't find any significant difference in the patients' characteristics, however, there could be confounding factors that we were unable to control for. Furthermore, we didn't use a formal ERAS pathway, although we followed most of its principles. The concept of ERAS was initially introduced in the 1990s as a means to improve postoperative recovery and shorten length of stay after colorectal surgery [30]. By its nature, ERAS is multimodal, multidisciplinary, requiring an important team commitment and may vary between centers according to local experience and expertise. In our study, we showed that a NOP protocol was easy to implement, with significant benefits in terms of patients' outcomes and direct cost. Finally, 40% patients in the NOP did receive some narcotics, although the morphine milligram equivalent was very low. We performed the analysis on an intention to-treat basis in order to account for this limitation. Further evaluation is required to evaluate the effects of the NOP protocol on the risk of postoperative opioid addiction.

5. Conclusion

In this study, we demonstrated the feasibility of the prospective implementation of a NOP protocol for patients undergoing RARC. Compared to a control group of patients who received the same procedure, patients included in the NOP protocol demonstrated a significant improvement regarding time to regular diet, reduction in the length of stay at hospital and reduction in direct costs within the 30-days after initial surgery. We believe this protocol is of interest for all patients who are candidates to major urological surgery and could provide benefits at the population level in the context of the national opioid crisis.

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