Initial experience with ketamine-based analgesia in patients undergoing robotic radical cystectomy and diversion

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Abstract

Introduction: We instituted a ketamine-predominant analgesic regimen in the peri- and postoperative periods to limit the effects of narcotic analgesia on bowel function in patients undergoing radical cystectomy. The primary end points of interest were time to return of bowel function, time to discharge, and efficacy of the analgesic regimen.

Methods: We performed a retrospective chart review of patients undergoing robotic-assisted laparoscopic cystectomy (RARC) with urinary diversion by a single surgeon at our institution from January 1, 2011 to June 30, 2012. Patients receiving the opioid-minimizing ketamine protocol were compared to a cohort of patients undergoing RARC with an opioid-predominant analgesic regimen.

Results: In total, 15 patients (Group A) were included in the ketamine-predominant regimen and 25 patients (Group B) in the opioid-predominant control group. Three patients (19%) in Group A discontinued the protocol due to ketamine side effects. The mean time to bowel movement and length of stay in Group A versus Group B was 3 versus 6 days ($p < 0.001$), and 4 versus 8 days, respectively ($p < 0.001$). Group A patients received an average of 13.0 mg of morphine versus 97.5 mg in Group B ($p < 0.001$).

Conclusions: Patients who received our ketamine pain control regimen had a shorter time to return of bowel function and length of hospitalization after RARC. Our study has its limitations as a retrospective, single surgeon, single institution study and the non-randomization of patients. Notwithstanding these limitations, this study was not designed to show inferiority of one approach, but instead to show that our protocol is safe and efficacious, warranting further study in a prospective fashion.

Introduction

Radical cystectomy and urinary diversion to manage bladder cancer carries a high morbidity. A common side effect is protracted ileus causing prolonged hospitalization.[1] A number of institutions have reported fast-track protocols designed to minimize postoperative ileus and shorten the length of stay in these patients.[2-6] A central theme in these protocols has been decreasing perioperative opioid analgesic. This focus has been justified based on the well-established relationship between opioids and bowel dysfunction.[7]

In September 2011, our institution altered our preferred post-cystectomy pain control regimen to minimize opioid usage. Our novel approach centered on the use of ketamine in the intraoperative and postoperative period. Ketamine is associated with decreased postoperative pain scores and cumulative morphine consumption.[8-11] Adjuvant analgesia included the use of a preoperative transversus abdominal plane (TAP) block, injection of local anesthetic to the incision, intravenous (IV), and oral acetaminophen and gabapentin. The aim of this pilot study was to assess the safety and efficacy of our multi-modal analgesic protocol in patients undergoing robotic-assisted cystectomy (RARC) and urinary diversion.

Methods

Design and analysis

Institutional review board approval was obtained to retrospectively review patients undergoing RARC with urinary diversion for urothelial carcinoma of the bladder by a single surgeon from January 1, 2011 to June 30, 2012. This time was selected as it encompassed our institution's transition to a ketamine-predominant analgesic program in these patients. The outcome of this group was compared to an immediately preceding group of patients undergoing the same procedure, but receiving opioid-predominant analgesia. These were patients treated in the interval between January 1, 2010 and January 1, 2011. All patients undergoing RARC by the single surgeon were included in the study, excluding patients with chronic pain or those deemed medically unable to receive ketamine analgesia as determined by our institution's Regional Anesthesia and Acute Pain team.

Our multimodal, ketamine predominant protocol is delineated by pre-, intra-, and postoperative plans to reduce or eliminate opioid use (Table 1). Patients received oral gabapentin and acetaminophen in the holding area. TAP blocks were also performed preoperatively by our anesthesiologists and involved an ultrasound-guided injection of local anesthetics into the neurovascular plane of the abdominal wall, providing analgesia to the abdominal wall by blocking the 7th to 11th intercostal nerves (T7-T11), the subcostal nerve (T12), the ilioinguinal nerve and iliohypogastric nerve (L1-L2).[12] Intra-operatively, patients were administered a general inhalation anesthetic and a continuous infusion of ketamine. The ketamine infusion was continued through the operation and into the postoperative period until the patient was tolerating oral administration (PO), at which time patients transitioned to oral ketamine. Oral gabapentin and acetaminophen were administered postoperatively regardless of PO status. "Breakthrough" opioid analgesics were defined as those administered when pain was not sufficiently controlled on the non-narcotic protocol. Patients were discharged with over-the-counter analgesics (e.g., ibuprofen or acetaminophen).

Operative technique

RARC with extended bilateral pelvic lymphadenectomy was performed using the da Vinci Surgical System (Intuitive Surgical, Inc.) A two-surgeon team used a 6-port transperitoneal approach. A single surgeon performed the extirpative portion and one of two fellowship-trained reconstructive surgeons performed the urinary diversion extracorporally. In cases of orthotopic bladder substitution, the robot was redocked for the urethral-intestinal anastomosis. Postoperative care (identical in both groups) included removal of the nasogastric tube at time of extubation, early and frequent ambulation beginning on postoperative day 0. Moreover, patients maintained their nothing by mouth (NPO) status until the return of their bowel function at which time diet was gradually advanced to general diet.

Statistical analysis

A comparison of group characteristics was made using the Kruskal-Wallis Chi-Square or Fisher's exact test. Time to first bowel movement and length of hospitalization were compared using Kaplan-Meier plots. Cox proportional hazards regression was used for univariate and multivariate tests predicting the time to bowel movement and discharge. Factors with p values less than 0.1 were considered in multivariate analysis. The analysis was then performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Table 1. Multimodal, ketamine predominant protocol

Preoperative	• Gabapentin (300 mg orally ×1), • Acetaminophen (1000 mg orally ×1), • Tranversus abdominis plane block*
Intra-operative	• Ketamine intravenously (5 mg/hr) glucose tolerance test • Acetaminophen (1000 mg intravenously every 6 hours) • Wound block (60 cc of 0.25% marcaine),
Postoperative	• Ketamine intravenously (5 mL/hr) transitioned to oral (20 mg orally every 6 hours)+ • Acetaminophen 1000 mg every 6 hours (intravenously or orally) • Gabapentin (300 mg orally every 8 hours) • "Breakthrough" opioid analgesics*

*At the discretion of urology team. +Managed by the Regional Anesthesia and Acute Pain team.

Results

A total of 40 patients were studied: 15 patients in Group A (non-opioid predominant protocol) and 25 in Group B (opioid-predominant protocol). Group characteristics were statistically equivalent, including age, sex, ASA (American Society of Anesthesiologists) classification, pre- and postoperative creatinine and hematocrit, operative time, amount of intra-operative fluids, blood products received, estimated blood loss, urinary diversion type, and utilization of neoadjuvant chemotherapy (Table 2).

Three patients from Group A had to discontinue the ketamine protocol due to side effects, including hypertension, blurred vision, and hallucinations. Unwanted symptoms resolved with discontinuation of ketamine and none of these patients had long-term adverse effects. Of the 15 that did complete the protocol, 10 patients (67%) utilized breakthrough opioids. Total opioid analgesia utilized (Table 3) during inpatient stay, however, was significantly less in Group A, with a median value of 13 mg versus 98 mg in the opioid-predominant group ($p < 0.001$). The median time to bowel movement was significantly less in Group A, 3 versus 6 days ($p < 0.001$). The median time to discharge was also significantly less in Group A at 4 days versus 8 days ($p < 0.001$). In multivariate analysis, opioid-predominant protocol was the only significant predictor of time to discharge. TAP blocks usage prior to the procedure did not appear to alter time to bowel movement or discharge in this patient population ($p = 0.8$ in both cases). No difference was noted in cause or frequency of hospital readmission rates (Table 4).

Discussion

Utilization of a ketamine predominant, opioid minimizing perioperative pain control protocol was a safe and effective way to manage intraoperative and postoperative pain in our RARC population. Decreased time to bowel movement and

Table 2. Patient demographics and operative data

	Group A: Non-opioid predominant (n = 15)	Group B: Opioid predominant (n = 25)	*p* value
Median age (yr)	68 (47–81)	68 (42–81)	0.83
Male (%)	12 (80)	17 (77)	1.00
ASA classification			
2	3 (20)	4 (18)	1.00
3	12 (80)	18 (82)	
Neoadjuvant chemotherapy (%)	11 (73)	12 (55)	0.25
Surgical pathology (%)			
T0	4 (27)	3 (14)	0.82
Ta	1 (7)	1 (5)	
Tis	2 (13)	3 (14)	
T1	0 (0)	1 (5)	
T2	6 (40)	6 (27)	
T3	0 (0)	2 (9)	
T4	1 (7)	2 (9)	
N+	1 (7)	4 (18)	
Median preoperative creatinine (mg/dL)	1.070 (0.78–2.76)	1.060 (0.66–2.05)	0.74
Median postoperative creatinine (mg/dL)	1.250 (0.91–2.02)	1.330 (0.86–2.61)	0.71
Median preoperative hematocrit (%)	38 (31–47)	39 (29–49)	0.83
Median postoperative hematocrit (%)	32 (24–39)	33 (26–44)	0.42
Median operative time (min)	373 (189–515)	421 (262–648)	0.03
Median EBL (mL)	250 (0–550)	300 (0–1000)	0.21
Median intra-operative IVF (mL)	3250 (1250–4800)	3500 (2200–7600)	0.05
Patients requiring intra-operative PRBC	0	2	0.51
Diversion type			
Ileal conduit	9 (60)	14 (63)	0.06
Indiana pouch	0 (0)	6 (23)	
Neobladder	6 (40)	3 (14)	

ASA: American Society of Anesthesiologists; EBL: estimated blood loss; IVF: intravenous fluids; PRBC: packed red blood cells.

hospital discharge were statistically significant when compared to our own historical control. While the differences in total operative time **and intravenous fluid consumption** (differences of less than 1 hour and 250 mL, respectively) were statistically significant, we do not believe that less than an hour of additional anesthetic could contribute to the additional 4 days of hospitalization seen in the control group. More importantly, total opioid consumption was the only statistically significant difference between patient groups on multivariate analysis.

A number of prior studies have reported strategies designed to reduce narcotic usage in patients undergoing cystectomy. Using a combination of ketorolac and celecoxib in their fast-track protocol, Pruthi and colleagues were able to reduce the time to bowel movement and discharge to 3 and 5 days, respectively.[3,4] In a recently published protocol, Saar and colleagues utilized oral diclofenac with epidural analgesia to minimize opioid utilization and impacts on bowel motility.[5] With this regimen, postoperative morphine equivalents were significantly reduced and attributed a low rate of gastrointestinal complications (6.4%) to this reduction.[5] Recently Lee and colleagues published a randomized trial of the mu opioid receptor blocker alvimopam in patients undergoing radical cystectomy, showing decreased postoperative ileus and length of stay.[13] While alvimopam works similar to ketamine-based approaches, it does not block

Table 3. Inpatient outcomes

	Group A: Non-opioid predominant (n = 15)	Group B: Opioid predominant (n = 25)	*p* value
Intravenous morphine equivalent (mg) Median (25th–75th percentile)	13.0 (2.0–50.0)	97.5 (61.5–161.4)	<0.001
Median days until bowel movement	3 (1–5)	6 (3–13)	<0.001
Median days until discharge	4 (3–13)	8 (5–14)	<0.001

Table 4. Readmissions in the global period based on primary diagnosis

	Group A: non-opioid predominant (n = 6; 40%)	Group B: opioid predominant (n = 11; 44%)	*p* value
Urinary tract infection, pyelonephritis, urosepsis	2	7	
Percent of readmissions	33%	64%	0.3
Wound complication			
Fascial dehiscence	1	1	
Pelvic abscess	–	2	
Percent of readmissions	17%	27%	1.0
Dehydration/electrolyte imbalances	2	1	
Percent of readmissions	33%	9%	0.5
Urinary tract obstruction, ureteroenteric obstruction, accidental stent removal	1	–	
Percent of readmissions	17%	0%	0.3

opioid effects on the respiratory or central nervous system.

Our limited success with these previously described protocols led us to look for another approach to decrease opioid usage. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to potentiate the effects of other analgesics, such as morphine, by reducing the development of tolerance to such opioids and by directing the analgesic actions of ketamine via monoaminergic, cholinergic and mu mechanisms.[14-19] Ketamine does not slow gut peristalsis as it acts at σ-opioid receptor sites, which are not found in the gastrointestinal tract.[20-22] Current clinical trials on the use of ketamine, in conjunction with opioids, for postoperative pain reveal a mixed picture. Carstensen and colleagues reviewed 11 randomized, double-blinded clinical trials of ketamine added to opioid for postoperative pain.[9] This review revealed 6 studies (n = 305) showing that adding ketamine to morphine resulted in improved postoperative analgesia (and a statistically significant decrease in morphine consumption), while 5 studies (n = 582) showed no improvement. Carstensen and colleagues found that the benefit of ketamine in decreasing opioid consumption following major abdominal surgery remains unclear. Furthermore, studies of ketamine in major urologic surgery (particularly in cystectomy) are scarce leading us to explore the effectiveness of ketamine in cystectomies at our institution.[23]

Overall, our ketamine-based protocol was generally well-tolerated and safe with rapid resolution of any adverse side effects with discontinuation. The primary undesirable side effects reported in the 17% of patients (n = 3) unable to complete the protocol included hypertension, blurred vision, and hallucinations. Side effects stopped immediately with the discontinuation of the protocol and no additional adverse events noted. The side effect rate, however, is higher than described in one systemic review, which showed that 8 out of 1210 patients treated with ketamine experienced side effects, including bad dreams and hallucinations.[10] A reduction in the side effects may be achieved by decreasing the ketamine dose in future investigations.

The nearly 90% reduction (98 to 13 mg) in median opioid analgesic use observed in our patients exceeds results previously reported.[9,10] This discrepancy is likely explained by the multi-modal nature of our protocol. The retrospective nature of this study precludes any determination of the relative roles of ketamine versus "adjuvant" pain control strategies in overall outcome. Gabapentin, acetaminophen, bilateral TAP blocks, and local anesthetic wound infiltration all provided adjuvant non-opioid analgesia. Inclusion of these additional components of our protocol is evidence-based. Results from randomized controlled trials and meta-analyses investigating the efficacy of gabapentin are varied; some demonstrate no difference, while others show a statistically significant reduction in opioid utilization postoperatively.[8] Intravenous acetaminophen has also been demonstrated to decrease postoperative opioid use in randomized control trials.[24] As the goal of this study was primarily to assess safety and difference in time to discharge between the non-opioid and opioid-predominant protocols, we did not directly assess post-discharge pain needs. The post-discharge pain regimen of over-the-counter analgesics was unchanged from patients on the opioid-predominant protocol.

The local analgesic component of our protocol included local anesthetic wound infiltration and bilateral TAP blocks. Recent reviews of TAP blocks demonstrate varying conclusions as to efficacy in treating postoperative pain. Some suggest these discrepancies exist due to the variety of surgeries utilizing TAP blocks, differences in technique, dose, and timing (pre- vs. postoperatively).[12] TAP blocks consistently reduce the amount of opioids consumed by the patient in the postoperative period.[8,25,26] However, in our study TAP blocks were introduced to our protocol after instituting this ketamine regimen, with only 50% (n = 8) of patients receiving them. Although we did not demonstrate that TAP blocks independently influenced time to return of bowel function or discharge, TAP blocks likely contributed to decreased overall opioid utilization due to the immediate effect in the postoperative period.

While this study is limited by its retrospective, non-contemporaneous nature and potential for unidentified selection bias, our findings are consistent with the known impacts of opioids on bowel function. In an attempt to limit bias, a well-defined time period was selected for review to ensure that the perioperative care was equivalent between groups. Nevertheless, a potential bias exists that cannot be eliminated based on the non-randomization and retrospective nature of the study design. The heterogeneous mix of patients and variations in preoperative care have confound-

ing factors, therefore blurring the effects of ketamine on opioid consumption and time to return to bowel function. This study, though, was not designed to show inferiority of one approach over another, but instead to show that this novel ketamine protocol is safe and efficacious. With initial data from this study and as our familiarity with the ketamine regimen grows, a randomized, prospective study comparing it to our historically opioid-predominant protocol would provide more evidence to the benefits of this novel approach. Validation of this protocol by other institutions is also needed to confirm that the ketamine-centred, opioid-minimizing regimen is practical and effective among other surgeons and institutions.

Conclusions

Multi-modal ketamine-based analgesia was safe and effective in the cystectomy and urinary diversion population. Patients who completed the protocol had significantly less opioid analgesic utilization, shorter time to return of bowel function, and shorter time to discharge than patients receiving opioid-predominant analgesia. A larger, prospective trial is needed to confirm these results.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

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