Prophylactic belladonna suppositories on anesthetic recovery after robotic assisted laparoscopic prostatectomy

Federica Scavonetto, MD,[1] David R. Lamborn, MD,[1] Joan M. Mccaffrey, RN,[1] Darrell R. Schroeder, MS,[2] Mattew T. Gettman, MD,[3] Juraj Sprung, MD,[1] Toby N. Weingarten, MD[1]

[1]Department of Anesthesiology, College of Medicine, Mayo Clinic, Rochester, Minnesota, USA
[2]Division of Biomedical Statistics and Informatics, College of Medicine, Mayo Clinic, Rochester, Minnesota, USA
[3]Department of Urology, College of Medicine, Mayo Clinic, Rochester, Minnesota, USA

SCAVONETTO F, LAMBORN DR, MCCAFFREY JM, SCHROEDER DR, GETTMAN MT, SPRUNG J, WEINGARTEN TN. Prophylactic belladonna suppositories on anesthetic recovery after robotic assisted laparoscopic prostatectomy. *Can J Urol* 2013; 20(3):6799-6804.

Introduction: *Two prospective trials have demonstrated prophylactic antimuscarinics following prostatectomy reduce pain from bladder spasms. Our practice adopted the routine administration of prophylactic belladonna and opium (B&O) suppositories to patients undergoing robotic assisted laparoscopic radical prostatectomy (RALP). The aim of this study is to determine if this change in clinical practice was associated with improvement of postoperative outcomes.*

Materials and methods: *The medical records of 202 patients that underwent RALP surgery who were or were not administered prophylactic B&O suppositories in the immediate postoperative period were abstracted for duration of anesthesia recovery, pain and analgesic use.*

Results: *Patient and surgical characteristics between groups were similar except B&O group were slightly older ($p = 0.04$) and administered less opioid analgesics ($p = 0.05$). There was no difference between groups in the duration of phase I recovery from anesthesia ($p = 0.96$). Multivariable adjustments for age, body mass index, American Society of Anesthesiologists physical status, and surgical duration were made, and again it was found that suppository administration had no association with phase I recovery times ($p = 0.94$). The use of antimuscarinic medication for bladder spams in the B&O group was less during phase I recovery ($p < 0.01$), but was similar during the first 24 hours ($p = 0.66$). Postoperative sedation, opioid analgesic requirements and pain scales were similar during phase I recovery and the first 24 postoperative hours. Hospital length of stay was similar.*

Discussion: *The introduction of prophylactic B&O suppositories at the immediate conclusion of RALP surgery was not associated with improvements of the postoperative course.*

Key Words: belladonna and opium suppository, prostate surgery, bladder spasm

Introduction

Robotic assisted laparoscopic prostatectomy (RALP) has become a common approach to surgically treat prostate malignancy. An important advantage of RALP over conventional retropubic radical proctectomy is less postoperative pain and shorter convalesce period.[1] The reduction of postoperative pain with RALP is secondary to smaller incisions. However, with both approaches, visceral pain arising from bladder spasms can be problematic in the early postoperative period.[2,3] Muscarinic antagonists have been successfully used to control postoperative bladder spasms following prostate surgery.[2,3] Lukasewycz et al,[2] reported that placement of an belladonna and opium (B&O) suppository prophylactically at the beginning of RALP surgery can reduce postoperative pain and opioid analgesic requirements. Based on that study, we instituted a practice change of prophylactic placement

Accepted for publication March 2013

Address correspondence to Dr. Toby N. Weingarten, 200 First Street, SW, Rochester, MN 55901 USA

of B&O suppository at the conclusion of all RALP surgeries. The primary aim of this retrospective study is to determine if this practice change is associated with a reduction of time to anesthetic recovery and readiness for discharge from phase I recovery.

Materials and methods

This retrospective study was approved by the Mayo Clinic Institutional Review Board. In an effort to reduce postoperative bladder spasms and the duration of phase I recovery from anesthesia, beginning in October 2011 all patients undergoing RALP surgery were prophylactically administered a B&O suppository (60 mg belladonna and 16.5 mg opium) at the conclusion of surgery and before emergence from general anesthesia. To assess the effectiveness of this intervention on phase I recovery time we compared the clinical course of 101 consecutive patients who underwent uncomplicated RALP surgery by a single surgeon were administered a prophylactic suppository and 101 patients who underwent RALP surgery by the same surgeon during the preceding period.

The electronic medical, surgical, and anesthetic records of these patients were abstracted for demographic variables; American Society of Anesthesiologist (ASA) physical status score; surgical duration; anesthetic technique; administration of opioid and nonopioid analgesics, antiemetics, and muscarinic antagonists during surgery, phase I recovery, and the first 24 hours following phase I recovery; postoperative pain and sedation scores; the duration of phase I recovery; and hospital length of stay. The dose of administered opioid analgesics was standardized into intravenous morphine equivalents using published guidelines.[4] Pain scores were obtained at regular intervals by hospital nursing staff using the standard verbal numeric rating pain scale from 0-10, where a score of 0 denotes no pain and 10 denotes worst pain imaginable.

Postoperative sedation was determined at regular intervals by hospital nursing staff using the Richmond Agitation Sedation Scale (RASS).[5,6] The RASS is a 10-point scale, with four levels of anxiety or agitation (+1 to +4, cumulating in combative [+4]), one level to denote a calm and alert state (0), and 5 levels of sedation (-1 to -5, culminating in unarousable [-5]). Phase I recovery duration was defined as the time the patient was admitted to the PACU until he met discharge criteria. Discharge criteria from the PACU to the standard postoperative surgical wards are determined by PACU nursing staff using a modified Aldrete discharge scoring system.[7] This modified system assess patient in five categories: motor activity (no motion, weak motion, active motion,); respiration (requires airway maintenance, maintains airway without support, coughs on command); systolic blood pressure (≥ 50 mmHg, ± 20 mmHG-50 mmHg, ± 20 mmHg of preanesthetic systolic blood pressure); consciousness (no response, responds to stimulation, fully awake); and oxygen saturation (≤ 92% or preoperative level with supplemental oxygen, ≥ 93% or preoperative level with supplemental oxygen, S_PO_2 ≥ of 93% or preoperative level without supplemental oxygen). Each assessment category is scored from 0-2. To meet discharge criteria the patient must have a score of ≥ 8 and not have a 0 score in any category. In addition patients must have an absence of any of four respiratory events: bradypnea (three episodes of < 8 respirations per minute); apnea (single episode of ≥ 10 seconds); oxyhemoglobin desaturations (three episodes of S_PO_2 < 90% or preoperative level); or pain-sedation mismatch (defined as a single episode of a RASS ≤ -2 and a numeric pain score > 5).[8] If any of these respiratory events were to occur, the patient must have a 60 minute period of time free from any further respiratory event before being discharged from phase I recovery. Lastly, patients must be normothermic, have adequate analgesia (numeric pain score ≤ 4) and patency of all catheters, drains and intravenous lines.

The anesthetic management of patients did not follow a strict protocol but typically consisted of a volatile anesthetic with the strong preference for the use of desflurane, administration of multiple antiemetics,[9] and use of nonopioid analgesics. Nondepolarizng muscle relaxants were used in all cases and were reversed with neostigmine and glycopyrrolate. Postoperative opioid analgesic management typically consisted of intravenous hydromorphone administered by PACU nursing staff and via a patient controlled analgesia device on the surgical ward followed by oral oxycodone. Treatment of postoperative bladder spasms in the PACU was achieved with the use of opioid analgesics as well as B&O suppositories. On the surgical ward spasms were treated with both B&O suppositories and oral oxybutynin.

Statistical analyses

Clinical and demographic variables were compared between patients who received prophylactic suppository versus those who did not using Student's t-test for continuous variables and the chi-square test (or Fisher's exact test) for categorical variables. The primary outcome for this study was phase I recovery time. In addition to a univariate analysis, a multivariable analysis was performed with duration of phase I recovery time as the dependent variable. The explanatory variables included in the multivariable model included prophylactic B&O suppositories, age,

TABLE 1. **Preoperative characteristics of patients undergoing robotic assisted laparoscopic prostatectomy**

Characteristic	B&O n = 100	Control n = 101	p value
Age (years)	61.8 ± 6.6	59.9 ± 6.5	0.04
Body mass index (kg/m^2)	29.0 ± 3.8	28.3 ± 4.2	0.21
ASA physical status			0.14
1	9	4	
2	78	89	
3	13	8	
4	0	0	
Preoperative use of opioids	4	8	0.24

Data presented as mean +/- standard deviation or number of patients.
ASA = American Society of Anesthesiologists; B&O = belladonna and opium suppository.

body mass index, ASA status, and surgical duration. The sample size for this study was determined under the assumption that the standard deviation of phase I recovery time is 50 minutes. Based on this assumption we determined that a sample size of n = 100 per group would provide statistical power (two-tailed, alpha = 0.05) of 80% to detect a mean difference of 20 minutes between those who received prophylactic suppository versus those who did not. P values ≤ 0.05 denoted statistical significance. All statistical analyses were conducted using JMP (version 7.0.1, SAS Institute Inc., Cary, NC, USA).

Results

From October 2011 through March 2012 one surgeon performed 101 uncomplicated RALP surgeries in patients that received a prophylactic B&O suppository at the end of surgery prior to emergence from anesthesia. These patients were compared to a 101 patients who did not receive a prophylactic suppository and underwent RALP surgery by the same surgeon during the period preceding this practice change. One patient in the prophylactic group was excluded because at the time of surgery he also underwent a panniculectomy. Preoperative characteristics between the prophylactic and control groups were similar except that the prophylactic patients were slightly older (p = 0.04), Table 1. Most patients in both groups had overall good health as evidenced that 89.6% of the cohort had ASA-PS ≤ 2.

TABLE 2. **Surgical duration and intraoperative anesthetic management of patients undergoing robotic assisted laparoscopic prostatectomy**

Characteristic	B&O n = 100	Control n = 101	p value
Surgical duration (minutes)	197 ± 44	209 ± 46	0.07
Anesthetic management			
Morphine equivalents (mg)	35.9 ± 9.7	38.5 ± 9.6	0.05
Nonopioid analgesics*	50	48	0.78
Desflurane anesthetic	89	90	0.36
Multiple antiemetics†	70	64	0.19

Data presented as mean ± standard deviation or number of patients.
B&O = belladonna and opium suppository.
*Nonopioid analgesics were usually administered in the last 10 minutes of surgery and included intravenous 15 mg-30 mg ketorolac (40 B&O patients versus 39 Control patients, p = 0.78); intravenous 10 mg-30 mg ketamine (14 B&O patients versus 11 Control patients, p = 0.52); and one intravenous 1000 mg acetaminophen in a B&O patient.
†Antiemetic protocol consisted of intravenous 0.625 mg droperidol and 4 mg-8 mg dexamethasone at the beginning of surgery and 4 mg ondansetron during the last 10 minutes of surgery.

TABLE 3. **Course of phase I recovery from anesthesia in patients undergoing robotic assisted laparoscopic prostatectomy**

Characteristic	B&O n = 100	Control n = 101	p value
Recovery duration (minutes)	81 ± 36	81 ± 41	0.96
Rescue opioid analgesics	53	63	0.17
Morphine equivalents (mg)*	7.3 ± 4.5	8.0 ± 5.6	0.47
Rescue antiemetics	4	5	0.74
Rescue B&O	4	28	< 0.01
Richmond Agitation Sedation Scale			
Admission	-1 [-2, 0]	-1 [-1, 0]	0.13
Lowest	-1 [-1.75, 0]	-1 [-1, 0]	0.21
Dismissal	0 [-1 ,0]	0 [-1, 0]	0.35
Highest pain score†	3.7 ± 2.7	4.1 ± 2.9	0.38

Data presented as mean ± standard deviation, median [25% quartile, 75% quartile], or number of patients.
B&O = belladonna and opium suppository.
*Mean dose represents only those patients who were administered opioid analgesic.
†Pain score was determined from a standard 11 point numeric pain score where a score of 0 denotes no pain and 10 denotes worst pain imaginable.

The surgical and anesthetic course between groups were similar except that the prophylactic group received less opioid analgesics (p = 0.05) and trended towards having a shorter operations (p = 0.07), Table 2. Variations in the anesthetic management including the use of nonopioid analgesics were similar between the two groups, Table 2.

The patient course in the PACU including time to readiness for discharge from phase I recovery was similar between the two groups, Table 3. The number of patients who required rescue opioid analgesics and antiemetics were similar. Sedation and pain scores were also similar. There were no major complications during phase I recovery including the need for unplanned use

TABLE 4. **Hospital course of patients undergoing robotic assisted laparoscopic prostatectomy**

Characteristic	B&O n = 100	Control n = 101	p value
Length of stay (days)	1 [1, 1]	1 [1, 1]	0.51
Rescue opioid analgesics*	53	63	0.20
Morphine equivalents (mg)*†	8.3 ± 8.2	10.6 ± 18.2	0.31
Rescue antiemetics*	5	3	0.50
Bladder spasm treatment*	67	64	0.66
B&O suppository	18	28	0.13
Oxybutynin	63	60	0.66
Highest pain score*‡	3.8 ± 2.1	3.5 ± 1.9	0.34

Data presented as mean ± standard deviation, median [25% quartile, 75% quartile], or number of patients.
B&O = belladonna and opium suppository.
*Events that occurred within the first 24 hours following discharge from phase I anesthetic recovery to the postsurgical ward.
†Mean dose represents only those patients who were administered opioid analgesic.
‡Pain score was determined from a standard 11 point numeric pain score where a score of 0 denotes no pain and 10 denotes worst pain imaginable.

of non-invasive ventilation (e.g., CPAP) administration of naloxone or flumazenil for oversedation, or admission to an intensive care unit. The frequency of rescue B&O suppository administration was less in the prophylactic group. However, the rates of administration of suppositories or oxybutynin were similar in the first 24 hours following discharge from the PACU, Table 4. Similarly, pain and sedation scores, and analgesic and antiemetic requirements were similar. There were no major complications in either group and hospital length of stay was the same.

Potential association of the suppository on anesthesia recovery times was reassessed with the adjustment for age, body mass index, ASA status, and surgical duration. Again it was found that administration of the suppository had no significant association on phase I recovery after anesthesia ($p = 0.94$).

Discussion

The main finding of this retrospective review is that a practice change of routine placement of B&O suppositories at the conclusion of RALP surgery was not associated with a reduction of phase 1 anesthetic recovery. Further, this practice change was not associated with reduced use of rescue opioid analgesics, numeric pain scores, sedation scores, postoperative nausea and vomiting, or hospital length of stay. The use of prophylactic B&O suppositories was associated with a reduction of pharmacologic treatment of bladder spasms in the recovery room, but no reduction of bladder spasms requiring treatment within the first 24 hours.

Bladder spasms result from detrusor muscle contractions and are mediated by the sacral parasympathetic nerves. Both muscarinic receptor subtypes 2 and 3 have been implicated in painful bladder disorders and anticholinergic medications have been first line agents in their treatment.[10] Both sublingual oxybutynin and B&O suppositories have been shown to reduce postoperative bladder spasm pain and opioid requirements in patients undergoing prostate surgery.[2,3] The lack of clinical improvement following our practice change of prophylactic placement of B&O suppositories compared to the results reported by Lukasewycz et al[2] may be related to timing of suppository administration. We placed the suppository at the end of surgery while they placed it at the beginning. Optimal timing of B&O suppositories to prevent spasms or the time to peak concentration in bladder tissue of atropine or scopolamine from rectally administered belladonna has not been previously reported. Earlier placement of the suppository could allow sufficient time to work and may explain their more favorable result. However, if the clinical effects of these suppositories were delayed, we would expect a reduction in number of treatments for spasms in the first 24 postoperative hours, which was not observed. Tauzin-Fin et al[3] reported that prophylactic subinguinal oxybutynin administered after emergence from surgery and scheduled administration within the first postoperative day reduced spasms. Another difference between our results and those reported by Lukasewycz et al[2] include the frequent administration of intraoperative nonopioid analgesics in our clinical practice. These medications have well known opioid sparring effects and could have masked any benefit from the suppository. However, use of these medications was similar between groups and a post-hoc analysis found their use was not associated with a reduction in phase I recovery time or rescue opioid use (data not shown). Alternatively, the Tauzin-Fin[3] study reported the use of gabapentin, magnesium sulfate, wound infiltration with local anesthetic and acetaminophen as nonopioid analgesics.

This study was designed to examine the effects of a practice change on clinical practice and has all the inherent limitations of a retrospective study. Clinical decisions in regards to anesthetic management were left to the discretion of the attending anesthesiologist which was a source of potential bias; however variations in practice were evenly distributed between groups. A considerable strength of this review is that all patients in this cohort had the same surgery performed by a single surgeon.

Conclusion

In conclusion, we found no evidence that this practice change had any association with meaningful clinical improvements. This negative study suggests that confirmatory prospective evaluations of the use of prophylactic antimuscarinic drugs to prevent post-proctectomy bladder spasms are needed. Specifically, optimal timing of administration as well as best agents should be evaluated.

Disclosure

Support was provided solely from institutional and departmental sources (Departments of Anesthesiology and Urology, Mayo Clinic, Rochester, MN, USA). □

References

1. Hu JC, Wang Q, Pashos CL, Lipsitz SR, Keating NL. Utilization and outcomes of minimally invasive radical prostatectomy. *J Clin Oncol* 2008;26(14):2278-2284.

2. Lukasewycz S, Holman M, Kozlowski P et al. Does a perioperative belladonna and opium suppository improve postoperative pain following robotic assisted laparoscopic radical prostatectomy? Results of a single institution randomized study. *Can J Urol* 2010; 17(5):5377-5382.
3. Tauzin-Fin P, Sesay M, Svartz L, Krol-Houdek MC, Maurette P. Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy. *Br J Anaesth* 2007;99(4):572-575.
4. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th edition. Skokie, Illinois, American Pain Society, 1999.
5. Sessler CN, Gosnell MS, Grap MJ et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002;166(10):1338-1344.
6. Sessler CN, Grap MJ, Brophy GM. Multidisciplinary management of sedation and analgesia in critical care. *Semin Respir Crit Care Med* 2001;22(2):211-226.
7. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970;49(6):924-934.
8. Gali B, Whalen FX, Schroeder DR, Gay PC, Plevak DJ. Identification of patients at risk for postoperative respiratory complications using a preoperative obstructive sleep apnea screening tool and postanesthesia care assessment. *Anesthesiology* 2009;110(4):869-877.
9. White PF, O'Hara JF, Roberson CR, Wender RH, Candiotti KA. The impact of current antiemetic practices on patient outcomes: a prospective study on high-risk patients. *Anesthesia and Analgesia* 2008;107(2):452-458.
10. Chapple CR, Yamanishi T, Chess-Williams R. Muscarinic receptor subtypes and management of the overactive bladder. *Urology* 2002(5);60:82-88.