Does a perioperative belladonna and opium suppository improve postoperative pain following robotic assisted laparoscopic radical prostatectomy? Results of a single institution randomized study

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Introduction: *Robotic assisted laparoscopic radical prostatectomy (RALP) is a common treatment for localized prostate cancer. Despite a primary advantage of improved postoperative pain, patients undergoing RALP still experience discomfort. Belladonna, containing the muscarinic receptor antagonists atropine and scopolamine, in combination with opium as a rectal suppository (B & O) may improve post-RALP pain. This study evaluates whether a single preoperative B & O results in decreased postoperative patient-reported pain and analgesic requirements.*

Materials and methods: *Patients undergoing RALP at Virginia Mason Medical Center between November 2008 and July 2009 were offered the opportunity to enter a randomized, double-blind, placebo-controlled trial. Exclusion criteria included: glaucoma, bronchial asthma, convulsive disorders, chronic pain, chronic use of analgesics, or a history of alcohol or opioid dependency. Surgeons were blinded to suppository placement which was administered after induction of anesthesia. All patients underwent a standardized anesthesia regimen. Postoperative pain was assessed by a visual analog scale (VAS) and postoperative narcotic use was calculated in intravenous morphine equivalents.*

Results: *Ninety-nine patients were included in the analysis. The B & O and control groups were not significantly different in terms of age, body mass index, operative time, nerve sparing status or prostatic volume. Postoperative pain was significantly improved during the first two postoperative hours in the B & O group. Similarly, 24-hour morphine consumption was significantly lower in patients who received a B & O. No adverse effects secondary to suppository placement were identified.*

Conclusion: *Preoperative administration of B & O suppository results in significantly decreased postoperative pain and 24-hour morphine consumption in patients undergoing RALP.*

Key Words: carcinoma, analgesia, prostate, robotic

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Introduction

More than 200,000 radical prostatectomies are performed each year for localized prostate cancer in the United States alone.[1] The last decade has seen a marked increase in the use of minimally invasive techniques such as robotic assisted laparoscopic prostatectomy (RALP).[2,3] In many communities, robotic technology is utilized in most, if not all radical prostatectomies.[4]

A primary advantage of RALP over conventional surgical approaches is reduced postoperative pain. Nevertheless, patients undergoing RALP still experience discomfort. Optimal perioperative pain management for RALP has yet to be described.

Discomfort associated with RALP likely arises from two sources: incisional pain and bladder spasms. In particular, bladder spasms result from operative manipulation of the bladder, urethral division, urethra-vesicle anastomosis, and the postoperative presence of an indwelling urethral catheter. The pain resulting from such spasms are often resistant to conventional narcotic based pain management.[5]

Muscarinic receptor antagonists have been used successfully for the management of overactive bladder and for catheter-related discomfort.[6,7] Belladonna and opium (B & O) suppositories contain the naturally occurring muscarinic antagonists atropine and scopolamine and are often used in the perioperative setting of urologic surgeries to control severe bladder spasms.[8] The combined antimuscarinic and analgesic actions of B & O suppositories make them a potentially valuable agent for the treatment of postoperative pain and bladder spasms following RALP.

We hypothesize that administration of a B & O suppository at the time of anesthesia induction will result in improved postoperative pain as measured by morphine consumption and visual analog scale (VAS).

Materials and methods

All patients undergoing RALP at Virginia Mason Medical Center between November 1, 2008 and July 30, 2009 were offered the opportunity to participate in this randomized double-blind placebo-controlled clinical trial (VM IRB# 08100). Power analysis indicated that, to detect a 20% difference in 24-hour morphine consumption (0.05 level of significance and power of 0.80), a minimum of 23 patients would be required in each treatment group. A randomization schedule was developed using Research Randomizer.[9]

Patients were required to meet American Society of Anesthesiology (ASA) physical status class I-III and were able to give informed written consent. Exclusion criteria included risk factors for complications from anticholingeric agents (i.e. asthma, glaucoma), a history of adverse reaction to belladonna or opioid analgesics, a history of chronic pain or chronic analgesic use, or a history of substance dependency.

After anesthesia induction, patients were randomized to receive either a belladonna 16.2 mg and opium 60 mg suppository (Paddock Laboratories, Minneapolis, MN, USA) or digital rectal examination (DRE) in lieu of suppository (placebo). Suppository placement or DRE was performed by the circulating operating room nurse; operating surgeons, PACU nurses and the hospital care team were blinded as to suppository placement.

All patients received a standardized anesthesia protocol. Patients were premedicated 10 minutes prior to induction with midazolam 2 mg. Approximately 2 minutes prior to induction, patients were administered a dosage of 30 µg/kg morphine based on lean body weight. Induction included 2 mg/kg propofol. Muscle relaxation and tracheal intubation was facilitated with succinylcholine 1.5 mg/kg and anesthesia was maintained with isoflurane. Muscle relaxation was supplemented as necessary with cisatracurium to maintain adequate surgical relaxation. At the conclusion of surgery, neuromuscular blockade was fully reversed with neostigmine 0.07 mg/kg and glycopyrrolate 0.01 mg/kg.

Robotic assisted laparoscopic prostatectomy was performed as previously described[10] with the da Vinci surgical system by one of three surgeons. A total of five ports were utilized whether using a standard da Vinci system, da Vinci S, or da Vinci Si. Preoperative counseling, nerve sparing status, and individual intraoperative decisions were made at the discretion of the operating surgeon, each surgeon performed anterior approaches to the bladder. Postoperative pain was managed by the primary surgical service.

Postoperative pain management was provided via a patient-controlled analgesia (PCA) pump programmed to deliver 1 mg morphine every 8 minutes with no basal infusion. In the PACU, additional analgesia was administered via morphine bolus at the discretion of the PACU nurse or upon the patient request. Once on the ward, patients who rated their pain on a visual analog score (VAS) as 5 or higher had their PCA doses increased by 0.5 mg, to 1.5 mg every 8 minutes. For persistent pain despite this increased dose, PCA dosing frequency was shortened to 7 minutes. Once a patient was able to tolerate oral intake, the PCA pump was discontinued and the patient transitioned to oral pain medication in the form of oxycodone 5 mg, 1-2 tablets every 4 hours.

For purposes of analysis, oxycodone use was converted to intravenous morphine equivalents, using the following conversion method: oxycodone 1.5 mg oral = 1 mg morphine oral and 3 mg morphine oral = 1 mg morphine intravenous.[11] Similarly, the opioid component of the B & O suppository was converted to intravenous morphine equivalents using the formula 60 mg opium = 6 mg PO/PR morphine = 2 mg intravenous morphine. Using this formula, all opioid agents were

converted into morphine equivalent units and counted toward 24-hour total morphine consumption. Hospital based cost of B & O suppositories is $17.50 morphine hospital based cost is $10.00 per 50 mg.

Postoperative morphine consumption was recorded by nursing staff and verified using the electronic medical record. Where discrepancies were found, the electronic entry was used. The PCA priming dose could not be determined for two patients, one in the B & O group and one in the control group. For purposes of analysis, the highest possible priming dose (2 mg) was assumed for the patient in the B & O group, and the lowest possible dose (1 mg) was assumed for the control subject, thus biasing against the primary study hypothesis.

A 10 cm visual analog scale (VAS) with endpoints labeled "no pain" (0) and "worst possible pain" (10) was used to evaluate the efficacy of analgesia. Pain was assessed with patients at rest (VAS-R) postoperatively every hour for the first 4 hours, then every 2 hours for the next 8 hours, then every 4 hours for the next 12 hours (24 hours total). Pain was also assessed after standard mobilization (VAS-M) at the same time intervals by asking each patient to perform two maximal inspirations before indicating his level of pain on the VAS scale.

Patients were monitored for adverse effects of treatment including sedation, nausea and pruritus. Sedation was assessed every hour for the first 4 hours, then every 2 hours for the next 8 hours, then every 4 hours up to a total of 24 hours postop using a five-point modified sedation scale (0 = alert and oriented, 1 = awake but drowsy, 2 = sleeping but arousable by verbal commands, 3 = sleeping but arousable by tactile stimuli, and 4 = comatose). Nausea and pruritus were assessed at the same intervals via VAS. Two 10 cm visual analog scale (VAS) with endpoints labeled "no nausea" or "no itching"(0) and "worst possible nausea" or "worst possible itching" (10) were used to evaluate these potential side effects. All entries recorded on the VAS scales were measured in millimeters by the same provider.

TABLE 1. **Patient demographics, preoperative and intraoperative factors**

	B & O (n = 41)	**Control (n = 58)**	**p value**
Age (yr)	62 ± 7	61 ± 7	0.532
BMI	29 ± 5	28 ± 3	0.225
Preop AUASS	7 ± 5	9 ± 8	0.174
Operative time (min)	153 ± 26	155 ± 32	0.704
EBL (mL)	175 ± 172	143 ± 154	0.333
Intraoperative morphine (mg)	10 ± 1	10 ± 1	0.643
Prostate volume	59 ± 22	56 ± 16	0.341
Preop PSA	6 ± 3	5 ± 2	0.289
Diabetes mellitus			
Yes	6	4	
No	35	54	0.212
Clinical stage			
T1c	29	38	
T2a	12	20	0.589
Nerve sparing			
Unilateral	6	13	
Bilateral	24	36	
None	11	9	0.370
Surgeon			
JC	20	31	
PK	10	19	
CP	11	8	0.268

Data are mean ± standard deviation
BMI = body mass index; DM = diabetes mellitus; PSA = prostate specific antigen; AUASS = American Urologic Association Symptom Score; EBL = estimated blood loss; Prostate Volume is based on final pathologic specimen.

TABLE 2. **Pain assessment by visual analog scale (mm) at rest (VAS-R)**

Postop hour	B & O	n =	Control	n =	p value
1	32.53 ± 22	38	43.11 ± 26	54	0.043
2	26.5 ± 21	36	37.81 ± 23	54	0.02
3	22.25 ± 20	36	25.69 ± 20	51	0.431
4	19.15 ± 17	40	19.88 ± 17	56	0.835
6	14.85 ± 15	40	17.75 ± 17	56	0.39
8	11.17 ± 12	41	16.3 ± 16	56	0.082
10	10.6 ± 13	40	13.98 ± 14	55	0.231
12	9.28 ± 11	40	14.19 ± 16	57	0.093
16	11.59 ± 10	41	16.49 ± 16	55	0.084
20	15.97 ± 12	38	15.68 ± 13	53	0.915
24	13.84 ± 9	25	19.08 ± 18	40	0.188

Data are mean ± standard deviation

All data were analyzed using standard statistical software (SPSS for Windows, release 16.0, Chicago, IL, USA). For all analyses a p value < 0.05 was considered statistically significant.

Results

One-hundred and thirty-five patients signed informed consent for the study; however, 36 consented subjects were later excluded due to inadvertent administration of non-protocol anesthetic medication (16), incomplete data collection (9), surgery cancellation (4), withdrawal of consent (3), medication allergy (3), and identification of unrecognized alcohol abuse (1). Of the 99 evaluable patients, 41 were randomized to the B & O group and 58 to the control group.

Patient demographics, preoperative variables, and intraoperative processes are shown in Table 1. The B & O and control groups were not significantly different in terms of age, body mass index, operative time, nerve sparing status or prostatic volume.

Postoperative VAS pain scores are presented in Tables 2 and 3. Mean VAS-R and VAS-M assessments at each time interval were consistently lower in the B & O group compared to the control group, although this difference was statistically significant only for VAS-R

TABLE 3. **Pain assessed by visual analog scale (mm) after mobilization (VAS-M)**

Postop hour	B & O	n =	Control	n =	p value
1	32.62 ± 22	34	41.37 ± 24	51	0.094
2	28.30 ± 19	33	36.48 ± 23	52	0.095
3	23.92 ± 21	36	27.66 ± 22	50	0.425
4	19.13 ± 15	40	19.92 ± 16	51	0.807
6	16.25 ± 14	40	18.24 ± 18	55	0.562
8	14.05 ± 15	51	16.84 ± 17	56	0.395
10	13.25 ± 17	40	14.4 ± 15	55	0.725
12	10.75 ± 15	40	14.09 ± 16	57	0.303
16	11.2 ± 12	41	17.56 ± 19	55	0.06
20	17.41 ± 15	37	17.82 ± 15	51	0.418
24	18.84 ± 12	25	18.97 ± 17	36	0.973

Data are mean ± standard deviation

TABLE 4. **Mean morphine consumption (mg) by time interval**

Postop hour	B & O	n =	Control	n =	p value
0-1	5.42 ± 4.8	38	7.06 ± 8.6	54	0.250
1-4	6.48 ± 8.0	41	9.38 ± 7.1	56	0.064
5-8	5.08 ± 6.4	40	6.26 ± 6.3	56	0.362
9-12	4.9 ± 8.8	41	3.90 ± 4.2	56	0.457
13-16	3.7 ± 4.6	41	5.43 ± 5.2	56	0.093
17-20	5.22 ± 6.7	39	5.05 ± 5.5	55	0.897
21-24	3.81 ± 2.9	24	4.24 ± 3.8	38	0.641
Total 24	25.91 ± 19.08	41	37.47 ± 24.33	58	0.013

Data are mean ± standard deviation

assessments at postoperative hours 1 and 2 (p = 0.043 and 0.02, respectively).

The mean morphine consumption in each time interval was consistently lower in the B & O group compared to the control group, Table 4, although these differences were not statistically significant. Total 24-hour morphine consumption, however, was significantly lower in patients who received B & O suppository compared to those who did not (25.9 mg versus 37.5 mg, p = 0.013).

Hospital costs for IV morphine were equivalent between both groups since PCA morphine is administered in 50 mg/50 mL quantities and any unused portions were discarded.

Sedation, nausea and pruritus were similar between groups; no adverse effects from B & O suppository placement were identified (data not shown).

Discussion

In this randomized, double-blind, placebo-controlled trial, the preoperative administration of a B & O suppository resulted in a significant reduction in both 24-hour total morphine consumption as well as patients' perceived pain during the first two hours following RALP. No adverse effects from B & O therapy were identified.

Post-RALP pain likely arises from two sources, port-site incisional pain and bladder spasm, itself a result of bladder and urethral manipulation.[12,13] During RALP, bladder manipulation is significant as the anterior peritoneal attachments to the bladder are completely mobilized, the urethra is divided and a bladder-uretheral anastomosis is fashioned. This manipulation leads to symptoms similar to overactive bladder: painful involuntary detrusor contractions, suprapubic pain and a sense of urinary urgency. Classically, such symptoms are poorly controlled with narcotic pain medication[5] although they can be managed successfully with antimuscarinic therapy.[6,12,13] The belladonna component of B & O suppositories contains atropine and scopolamine, both of which are muscarinic receptor antagonists and therefore act to inhibit involuntary bladder contractions mediated by the parasympathetic nervous system in response intraoperative bladder and urethral manipulation.[14,15] The opioid component of the B & O suppository likely yields only a minimal effect as the dose administered with each suppository is equivalent to 2 mg of intravenous morphine.

In our analysis, morphine consumption and pain at rest during the first 2 hours after RALP was significantly lower in the B & O group versus the control cohort. There was a suggestion of benefit (pain; morphine consumption) throughout the initial 24 postoperative hours; however, the differences only achieved statistical significance during anesthesia emergence and in the initial recovery period. Our impression is that once the patient is fully awake and aware of the presence of the foley catheter, he is better able to process and manage some expected discomfort. Similarly, although VAS-R was remarkably different in the initial 2 hour postoperative period, VAS-M was not significantly different between the two groups likely because most pain related to movement is incisional and unaffected by antimuscarinic agents.

Previous studies have proposed multiple unique adjuncts for treatment of postprostatectomy pain including transdermal lidocaine,[16] transdermal nicotine,[17] intravenous magnesium[18] and intrathecal morphine with and without clonidine.[19,20] Each of the above studies included patients undergoing open radical prostatectomies. Pain control issues in patients undergoing RALP are distinct from open procedures given the relative differences in degree of bladder mobilization, pneumoperitoneum and intraperitoneal approach.

In their elegant randomized control study, Tauzin-Fin et al[12] showed a significant decrease in catheter-related pain and tramadol consumption in patients who received post-prostatectomy sublingual oxybutinin, also a potent muscarinic antagonist. We believe the B & O suppository is superior to oral and sublingual antimuscarinics because it can be safely administered immediately before surgery and, thus, have its maximal effect during anesthesia emergence and recovery, presumably the time when bladder spasms are the most intense.

Overall, the cost of analgesia was greater in the B & O group based upon inpatient hospital pharmacy charges ($17.50 per suppository). The potential savings of decreased IV morphine use is mitigated by the fact that morphine is dispensed in 50 mg aliquots and all unused portions are discarded. Even when discounting this fact, the mean potential saving of 12 mg of morphine per patient ($2.40) results in an increased mean cost of $15.10 for patients receiving a B & O suppository.

Conclusion

Preoperative administration of B & O suppository results in significantly decreased total 24 hour morphine consumption and significantly decreased perceived pain at rest in the first two postoperative hours. □

References

1. DeFrances CJ, Hall, MJ. 2002 National Hospital Discharge Survey. Retrieved from website: http://www.cdc.gov/nchs/data/ad/ad342.pdf. May 21, 2004.
2. Hu JC, et al: Patterns of care for radical prostatectomy in the United States from 2003 to 2005. J Urol 2008; 180: 1969-1974.
3. 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.
4. Munver R, Volfson IA, Kesler SS, Nazmy M, Sawczuk IS. Transition from open to robotic-assisted radical prostatectomy: 7 years experience at Hackensack University Medical Center. *J Robotic Surg* 2007;1(2):155-159.
5. McMahon SB, Dmitrieva, N, Koltzenburg, M. Visceral pain. *Br J Anaesth* 1995;75:132-144.
6. Agarwal A, Raza M, Singhai V et al. The efficacy of tolterodine for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Anesth Analg* 2005;101(4):1065-1067.
7. Agarwal A, Dhiraaj S, Singhal V, Kapoor R, Tandon M. Comparison of efficacy of oxybutynin and tolterodine for prevention of catheter related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Br J Anaesth* 2006;96(3):377-380.
8. Belladonna and Opium Suppository, [package insert]. Minneapolis, MN: Paddock Laboratories, INC., 1996.
9. Research Randomizer, Copyright ©1997-2010 by Geoffrey C. Urbaniak and Scott Plous; http://www.randomizer.org/; accessed 14 April 2009.
10. Sharma NL, Shah NC, Neal DE. Robotic-assisted laparoscopic prostatectomy. *Br J Cancer* 2009;101(9):1491-1496.
11. Bruera E, Belzile M, Pituskin E et al. Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. *J Clin Oncol* 1998;16(10):3222-3229.
12. 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.
13. Appell RA, Sand P, Dmochowski R et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. *Mayo Clin Proc* 2001;76(4):358-363.
14. Anderson KE. Pharmacology of lower urinary tract smooth muscles and penile erectile tissues. *Pharmacol Rev* 1993;45(3):253-308.
15. Andersson KE. Advances in the pharmacological control of the bladder. *Exp Physiol* 1999;84(1):195-213.
16. Habib AS, Polascik TJ, Weizer AZ et al. Lidocaine patch for postoperative analgesia after radical retropubic prostatectomy. *Anesth Analg* 2009;108(6):1950-1953.
17. Habib AS, White WD, El Gasim MA et al. Transdermal nicotine for analgesia after radical retropubic prostatectomy. *Anesth Analg* 2008;107(3):999-1004.
18. Tauzin-Fin P, Sesay M, Delort-Laval S, Krol-Houdek MC, Maurette P. Intravenous magnesium sulphate decreases postoperative tramadol requirement after radical prostatectomy. *Eur J Anaesthesiol* 2006;23(12):1055-1059.
19. Andrieu G, Roth B, Ousmane L et al. The efficacy of intrathecal morphine with or without clonidine for postoperative analgesia after radical prostatectomy. *Anesth Analg* 2009;108(6):1954-1957.
20. Brown DR, Hofer RE, Patterson DE et al. Intrathecal anesthesia and recovery from radical prostatectomy: a prospective, randomized, controlled trial. *Anesthesiology* 2004;100(4):926-934.