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Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy†

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Background. Bladder discomfort related to an indwelling catheter can exacerbate postoperative pain. It mimics overactive bladder syndrome that is resistant to conventional opioid therapy. Muscarinic receptor antagonists are effective for treatment of the overactive bladder. The aim of this study was to assess the efficacy of oxybutynin in the management of postoperative pain after radical prostatectomy.

Method. Forty-six ASA I or II men undergoing radical retropubic prostatectomy under general anaesthesia were randomly assigned to two groups, in a double-blind fashion: Group O and Group P (n=23 each). Group O and Group P received, respectively, sublingual oxybutynin 5 mg or placebo every 8 h during the 24 h after surgery. A 16F Foley catheter was placed during the vesico-urethral anastomosis and the balloon inflated with 10 ml of saline. Pain was assessed in the recovery room starting 10 min after extubation using a 100-point visual analogue scale (VAS). The patients were asked to specify whether pain was related to the surgical incision or bladder pain. Standardized postoperative analgesia included acetaminophen and tramadol administered via a patient-controlled analgesia system.

Results. The incidence of bladder catheter pain was 65% (15 of 23 patients) in Group P compared with 17% (4 of 23 patients) in Group O ($P<0.01$). Overall VAS scores at rest were significantly lower in Group O. Cumulative tramadol consumption was 322.9(124.3) mg [mean(SD)] in Group P and 146(48) mg in Group O ($P<0.01$). No oxybutynin-related side-effects were reported.

Conclusions. Sublingual oxybutynin is an effective treatment for postoperative pain after radical retropubic prostatectomy and produces a significant reduction in tramadol requirements.

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After major surgery, a bladder catheter is generally left *in situ* in order to avoid bladder distension and bladder-related pain,[1] and to allow urine output assessment. Moreover, bladder catheterization after radical prostatectomy is required to reduce the risk of urethral fistula.[2]

Bladder catheterization induces bladder irritation whose symptoms (urge to void and discomfort in the suprapubic region) are similar to the symptoms of an overactive bladder (urinary frequency and urgency with or without urge incontinence), caused by involuntary contractions of the bladder mediated by muscarinic receptors.[3] This catheter-related bladder discomfort exacerbates postoperative pain because of the abdominal wound and is resistant to conventional therapy.[1] Muscarinic receptor antagonists, such as oxybutynin, have been successfully used for the management of overactive bladder[4] and of catheter-related bladder discomfort.[5] The aim of this study was to evaluate the efficacy of oxybutynin in the management of postoperative pain after radical retropubic prostatectomy.

†This study was presented, in part, at the 2006 ASA meeting in Chicago, USA.

Methods

The study was approved by the local Research Ethics Committee and informed consent was obtained from all patients. Forty-six ASA I or II men undergoing radical retropubic prostatectomy under general anaesthesia were recruited to the prospective, randomized, double-blinded, and placebo-controlled study. Patients were taught how to use the patient-controlled analgesia system (PCAS) before operation. A standardized, horizontal, 100 mm linear visual analogue scale (VAS) was used for pain assessment at rest (0=no pain, 100=unbearable pain). Patients were instructed about bladder catheterization and the risk of catheter-related discomfort (defined as urge to void) and incisional pain (defined as discomfort in the suprapubic region). Incisional and catheter-related pains were assessed. Exclusion criteria were inability to use the PCAS, a history of chronic pain or long-term use of opioids, bladder outflow obstruction, an overactive bladder (frequency, >3 times in the night or >8 times per 24 h), and central nervous system, cardiovascular hepatic or psychiatric disease.

Anaesthesia and postoperative analgesia

Patients were pre-medicated with oral gabapentine 600 mg (used for its anti-hyperalgesic activity),[6] 1 h before surgery, and a standardized general anaesthesia was administered. Anaesthesia was induced using i.v. propofol 2.5 mg kg^{-1} and sufentanil 0.8 μg kg^{-1}, followed by 50 mg kg^{-1} body weight of magnesium sulphate (used as an anti-hyperalgesic *N*-methyl-D-aspartate blocker)[7] in 50 ml of isotonic saline solution for 20 min. Tracheal intubation was facilitated with cisatracurium 0.15 mg kg^{-1}. Anaesthesia was maintained with end-tidal sevoflurane at a concentration of 2–2.5% and a target-controlled infusion of sufentanil (0.2–0.4 ng ml^{-1}). Neuromuscular block was maintained by a continuous infusion of cisatracurium 3 mg h^{-1}. The patients were mechanically ventilated with a 50:50 air–oxygen mixture and ventilation was adjusted to keep the end-tidal carbon dioxide between 4.7 and 6 kPa. Isotonic saline was infused at 10–15 ml kg^{-1} h^{-1}. Heart rate, systolic, mean, and diastolic blood pressures, Sp_{O_2}, and oesophageal temperature were recorded at 5 min intervals throughout the surgical procedure. A colloid infusion (Elohes® 500 ml) was given when surgical blood losses were up to 500 ml. Normothermia was maintained with a forced warm air device throughout anaesthesia. During the vesico-urethral anastomosis the bladder was catheterized with a 16F Foley catheter and its balloon inflated with 10 ml of saline solution. The abdominal wound was infiltrated with ropivacaine 300 mg (40 ml). During wound closure, the infusions of sufentanil and cisatracurium were stopped, and an i.v infusion of acetaminophen 2 g and a loading dose of tramadol 100 mg were infused for 15 min.

Postoperative pain management and bladder discomfort assessment

After surgery, patients were transferred to the post-anaesthetic care unit (PACU) and were randomly assigned to one of the two groups receiving either oxybutynin 5 mg (Group O, n=23) or placebo (Group P, n=23) sublingually every 8 h for the first 24 h after surgery. Randomization was performed using a computer-generated randomization list. In the PACU, a staff anaesthetist, blinded to the assignment of the patients, was in charge of pain management. Ten minutes after extubation, patients received their sublingual medication and the PCAS was connected. The PCAS contained tramadol 8 mg ml^{-1} and droperidol 0.05 mg ml^{-1}, and was set to deliver a 16 mg bolus dose of tramadol (2 ml) with a 10 min lockout interval and no background infusion. We assessed the global pain score at rest using the VAS every 4 h for the first 24 h after surgery. During each evaluation, patients were asked to specify whether the pain experienced was related to the surgical wound (i.e. discomfort in the suprapubic region) or to the bladder catheter (i.e. associated with urge to void). In both cases, pain was defined as a VAS score >30. Tramadol consumption was noted every 4 h during the same period. In the two groups, i.v. acetaminophen 1 g was given as analgesic rescue, and metoclopramide 10 mg was administered i.v. as an anti-emetic drug when required. Sedation was assessed using a five-point scale (0=alert and 4=deep sleep). Duration of surgery, peroperative anaesthetic drug consumption, total and bolus doses of tramadol, and side-effects (such as sedation >2, nausea and vomiting, dry mouth, blurred vision, agitation, and tachycardia) were also recorded. Additionally, patients were asked to judge their satisfaction concerning pain management on a 10-point scale (0=not satisfied, 10=extremely satisfied), and to identify any problems related to oxybutynin administration.

Statistical analysis

In the absence of previous studies, we decided that a 20% difference in tramadol consumption between the two groups would be clinically relevant and assumed an SD of 20%. We calculated that 23 patients would be required in each group to detect this difference and unpaired t-test with α=0.05 and β=90%, estimated 23 patients in each group.

Data were expressed as mean (SD). Continuous variables were analysed using Student's t-test. Ordinal data (VAS values, sedation score, and tramadol consumption) were analysed using the Friedman test or repeated measures analysis of non-parametric data. Chi-squared test was used to analyse dichotomous data. A P-value of <0.05 was considered statistically significant.

Results

The two groups were similar with regard to patient characteristics, duration of surgery, intraoperative doses of

Table 1 Patient characteristics. Data are expressed as mean (SD), except for age which is given as mean (range)

	Group P (n=23)	Group O (n=23)
Age (yr)	61.1 (54–75)	65.8 (54–72)
Weight (kg)	78.1 (13.8)	74.1 (9.1)
Duration of surgery (min)	181.8 (33.8)	188.2 (31.3)
Intraoperative sufentanil (μg)	158.5 (28.6)	148 (30.2)
Intraoperative cisatracurium (mg)	15.4 (2.2)	16 (3)

sufentanil and cisatracurium, and time to extubation (Table 1). The mean (SD) cumulative dose of tramadol after 24 h was 146 (80) mg in Group O and 322.9 (124.3) mg in Group P ($P<0.001$) (Table 2). Analysis of tramadol consumption in each 4 h interval showed that patients in Group O consumed significantly less tramadol than those in Group P ($P<0.001$). The differences in tramadol consumption between the groups were constant over time (Fig. 1). Pain values at rest were significantly lower in those in Group O than those in Group P ($P<0.001$) throughout the study period (Fig. 2). No sedation was noted in any of the patients (score 1). Postoperative nausea occurred in four patients in each group after the first tramadol demand after starting the PCAS. This responded rapidly to i.v. metoclopramide. Seven patients in Group O required rescue analgesia compared with 18 patients in Group P ($P<0.05$).

The incidence of catheter-related bladder pain was significantly higher in Group P compared with Group O ($P<0.05$). The symptom 'urge to void' was reported by 18 patients in Group P compared with 4 in Group O ($P<0.05$). No patient in Group O reported a dry mouth. Patients' satisfaction scores were significantly higher in Group O than in Group P (Table 2), but four patients in Group O complained of being disturbed at night to be given oxybutynin.

Discussion

Our study is consistent with pain being derived from two mechanisms after radical retropubic prostatectomy. Pain because of the surgical wound can be managed with multimodal analgesia, including tramadol.[8] Postoperative pain because of an indwelling bladder catheter is well treated by muscarinic receptor antagonists.

This study shows that sublingual oxybutynin 5 mg every 8 h is effective for postoperative bladder catheter pain. During the 24 h study period, cumulative tramadol consumption was <65% in the oxybutynin group compared with the control group. The VAS pain scores were also significantly lower in the oxybutynin group, compared with the control group. No side-effects because of oxybutynin were reported.

The bladder receives cholinergic innervation from the pelvic nerves and adrenergic innervation from the hypogastric nerve. It has a heterogeneous population of muscarinic receptors with a predominance of the M2 muscarinic receptor subtype and fewer M3 receptors. M2 receptor activation causes contraction of detrusor smooth muscles,

Table 2 Postoperative events and tramadol consumption. Data are expressed as number of patients (%) or mean (SD). Patient satisfaction score is given as values that are expressed as median (interquartile range). NS, not significant

	Group P (n=23)	Group O (n=23)	P-value
Time to extubation (min)	41.1 (12)	46 (12)	NS
Number of patients with bladder catheter pain (%)	15 (65)	4 (17)	<0.01
Number of patients with surgical wound pain (%)	3 (13)	2 (9)	NS
Number of patients requiring paracetamol (%)	18 (78)	7 (30)	<0.05
Tramadol consumption per 24 h (mg)	322.9 (124.3)	146 (80)	<0.01
Patient satisfaction score	5 (4–5)	8 (7–9)	<0.001

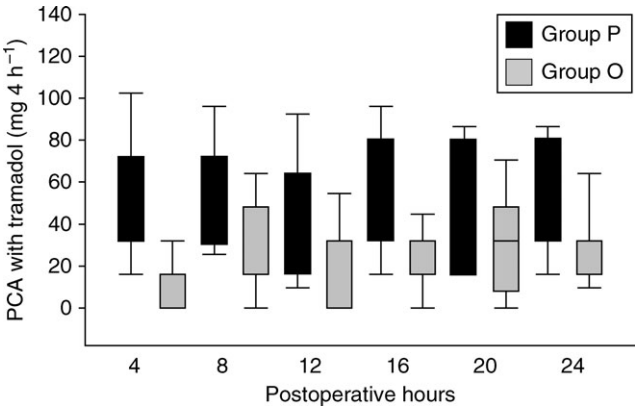

Fig 1 Box plot of median tramadol consumption during each 4 h interval. The error bars represent the interquartile range. The overall difference between the two groups was significant (Friedman test, $P<0.001$) and the tramadol consumption at each time point was significantly lower in Group O than in Group P (*post hoc* Dunn test, $P<0.05$).

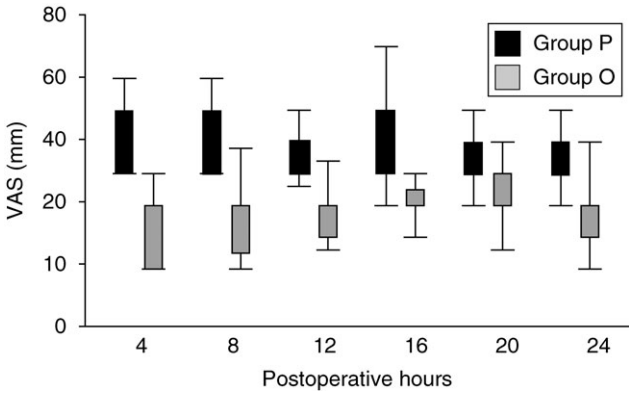

Fig 2 Box plot of median VAS scores at rest in the two groups. The error bars show the interquartile range. The difference between the two groups was significant (Friedman test, $P<0.001$) and the VAS at each time point was significantly lower in Group O than in Group P (*post hoc* Dunn test, $P<0.05$).

and selective M3 receptor inactivation leads to M2-mediated contraction of the detrusor muscle.[9 10] Catheter-related irritation can produce bladder pain (urge to void or discomfort in the suprapubic region). These symptoms are similar to symptoms of an overactive bladder (urinary frequency and urgency, with or without urge incontinence), which are caused by involuntary contractions of the bladder mediated by muscarinic receptors.[11] The triggers for muscarinic receptor stimulation are bladder catheter and the vesico-urethral anastomosis.

The incidence and severity of bladder discomfort have been analysed by Agarwal and colleagues.[12] They classified the severity of bladder discomfort as mild (reported by the patient only on questioning), moderate (reported by the patient without questioning), and severe (reported by the patient without questioning and accompanied by behavioural responses such as flailing limb, strong vocal response, and attempt to pull out the urinary catheter). These authors demonstrated the efficacy of oxybutynin in reducing the incidence (from 58 to 35%) and severity of bladder discomfort. However, they did not report fentanyl requirements for postoperative pain. A major difference between the study of Agarwal and colleagues and ours concerns the painful area. In their study of percutaneous nephrolithotomy, surgical access was not through the suprapubic region, allowing patients to differentiate postoperative pain from bladder discomfort. In our study, bladder discomfort and surgical wound pain are in the same area. This makes it difficult for the patients to distinguish the two types of discomfort. Bladder discomfort is a part of postoperative pain, and adequate treatment reduces VAS scores and tramadol requirements. The effective management of bladder discomfort prevents behavioural responses such as attempts to pull out the catheter and postoperative agitation that can be difficult to treat.[13]

Oxybutynin has a direct relaxant effect on the bladder because of its spasmolytic and antimuscarinic properties. It is a muscarinic M1/M3-selective antagonist and has a 10-fold higher affinity for M3 receptors than for M2 receptors. Therefore, oxybutynin acts directly on the primary M3 receptor responsible for detrusor contraction.[14] After oral oxybutynin 5 mg, the peak plasma level is reached after 1 h and the estimated half-life is <2 h with a duration of action of 6–10 h.[12] Oxybutynin can be given orally 1 h before induction of anaesthesia.[5 12] In our study, we preferred to administer oxybutynin by the sublingual route in the recovery room to avoid postoperative nausea and vomiting. Oral oxybutynin undergoes extensive hepatic and gastrointestinal first-pass metabolism that produces high serum concentrations of the active metabolite *N*-desethyl-oxybutynin.[15] This metabolite is responsible for the high incidence of dry mouth because of its action on the salivary glands where 90% of the muscarinic M3 subtypes are located. We observed no side-effects compared with a 52% incidence rate reported in the study of Agarwal and colleagues.[12]

Patient satisfaction scores were higher in the treatment group, supporting the importance of treating bladder discomfort. Transdermal oxybutynin patches (Oxytrol®, Watson Pharmaceuticals)[16] are now available and may be useful in reducing the postoperative bladder pain. Studies of this route of administration in the perioperative period would be warranted.

In conclusion, the postoperative pain after radical prostatectomy is mediated by both the surgical wound discomfort and catheter-induced bladder discomfort. Oxybutynin reduces bladder discomfort and is useful for postoperative pain management.

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