CURRENT THERAPEUTIC RESEARCH

VOLUME 73, NUMBER 6, DECEMBER 2012

Effect of Intraoperative Paracetamol on Catheter-Related Bladder Discomfort: A Prospective, Randomized, Double-Blind Study

Pinar Ergenoglu, MD[1]; Sule Akin, MD[1]; Oya Yalcin Cok, MD[1]; Evren Eker, MD[1]; Baris Kuzgunbay, MD[2]; Tahsin Turunc, MD[2]; and Anis Aribogan, MD[1]

[1]*Anesthesiology and Reanimation Department, Baskent University School of Medicine, Adana,Turkey; and* [2]*Department of Urology, Baskent University School of Medicine, Adana, Turkey*

ABSTRACT

BACKGROUND: The insertion of urinary catheters during urinary surgical interventions may lead to catheter-related bladder discomfort (CRBD) in the postoperative period.

OBJECTIVE: We aimed to evaluate the effect of single-dose intravenous paracetamol on CRBD.

METHODS: In this randomized, controlled, double-blind study, 64 patients (age >18 years, American Society of Anesthesiologists Physical Status I–II) requiring urinary bladder catheterization for percutaneous nephrolithotomy were assigned to groups that received either intravenous paracetamol (15 mg/kg) (group P) or NaCl 0.9% solution (control group [group C]) 30 minutes before the end of surgery. Patients received patient-controlled analgesia (10-mg bolus of meperidine, without infusion, 20-minute lock out) postoperatively. CRBD and pain status were assessed at

re meperidine

RESULTS: Group P had significantly lower CRBD scores at all time points except at 12 hours postoperatively compared with group C ($P < 0.05$). Total meperidine consumption was significantly higher in group C ($P < 0.05$). Patient and surgeon satisfaction scores were significantly higher in group P ($P < 0.05$).

CONCLUSIONS: Intraoperative single-dose paracetamol was found to be effective in reducing the severity of CRBD and pain in urologic surgery. We suggest that it may be an efficient, reliable, easy-to-apply drug for CRBD. ClinicalTrials.gov identifier: NCT01652183. (*Curr Ther Res Clin Exp.* 2012;73:186–194)

KEY WORDS: catheter-related bladder discomfort, intravenous paracetamol, urologic surgery.

Accepted for publication August 2, 2012.

http://dx.doi.org/10.1016/j.curtheres.2012.08.001

0011-393X

INTRODUCTION

The insertion of an urinary catheter in a patient undergoing a surgical procedure, especially urinary interventions, may lead to catheter-related bladder discomfort (CRBD) with varying degrees of severity during the postoperative period. CRBD symptoms associated with an indwelling urinary catheter are similar to overactive bladder (OAB) symptoms such as discomfort in the suprapubic region, urinary urgency, frequency, and a burning sensation with or without urge incontinence.[1,2]

The clinical appearance of CRBD and OAB are both associated with involuntary detrusor smooth muscle contractions, in which prostaglandins (PGs) have been reported to be responsible for low urinary tract function leading to micturition reflex by triggering bladder contraction.[3] The previous studies reported the incidence of CRBD as ranging from 50% to 90%.[2,4–6] The high incidence of patient discomfort may result in a prolonged hospital stay in the postoperative care unit. For this reason, the anesthesiologists should be aware of the symptoms of CRBD.

The goal of the various treatment options for CRBD has been to control involuntary urinary bladder contractions.[4] However, these therapies may also induce undesirable effects such as restlessness, agitation, and inadequate response to pain treatment, particularly in the early postoperative period.

Paracetamol is a drug with proven efficacy for the management of mild and moderate postoperative pain.[7] It inhibits PG synthesis.[8] Based on the same mechanism, the inhibiting effects of paracetamol on PG synthesis may also alleviate the symptoms of CRBD. To our knowledge, this is the first study is to evaluate the effect of intravenous paracetamol on CRBD. In this study, according to this common pathway, we aimed to address the effect of single-dose intravenous paracetamol on CRBD after percutaneous nephrolithotomy (PNL).

PATIENTS AND METHODS

After obtaining approval from the University Research Ethics Committee (Baskent University Research Ethics Committee, Ankara, Turkey, KA08/180) and written informed consent from the patients, 64 patients were included in this double-blind, randomized, controlled study. The study was completed in 12 months. The inclusion criteria were $\geq$18 years of age, American Society of Anesthesiologists Physical Status of I to II, undergoing PNL with a urinary bladder catheter. The exclusion criteria were obesity (body mass index $>$30), long-term opioid use, bladder outflow obstruction, benign prostatic hyperplasia, and OAB (frequency $>$3 times at night or $>$8 times within 24 hours). We used a computer-generated randomized number list for sealed envelopes. These envelopes were prepared by a nurse who was not associated with the study. The envelopes were opened by the anesthesia technician who prepared the study drugs.

The patients were randomly divided into 2 groups: group P (paracetamol group, n = 32) received 15 mg/kg paracetamol intravenously and group C (control group, n = 32) received 1.5 mL/kg 0.9% NaCl solution intravenously 30 minutes before the end of surgery. The study drugs were prepared, labeled, and covered with opaque paper in a drug preparation room and brought to operating theater before anesthesia induction by an anesthesiologist who was not part of the study. The anesthesiologist

who performed the anesthesia induction and maintenance was also blinded to the group allocation throughout the entire study period, including the first 24 hours postoperatively. All postoperative assessments and data recording were performed by an anesthesiologist blinded to patient allocation and study drugs.

A peripheral intravenous line was placed using an 18- or 20-gauge catheter in patients. No premedication was administered. Routine anesthesia monitoring was performed using 5-lead electrocardiography, noninvasive blood pressure measurement, and pulse oximetry. Anesthesia was induced with intravenous 3 to 5 mg/kg thiopental sodium and 1 μg/kg fentanyl, and endotracheal intubation was facilitated with vecuronium bromide 0.1 mg/kg. Anesthesia was maintained with mixture of isoflurane 1% to 2% and N_2O/O_2 (Fio_2, 50%). Additional muscle relaxants were administered when needed.

After induction of anesthesia, urinary catheterization was performed using an 18-French urinary catheter with patients in the lithotomy position; the catheter balloon was inflated with 10 mL of 0.9% NaCl. At the end of the surgery, all patients had a nephrostomy catheter, and infiltration of the insertion site with 20 mL 0.25% bupivacaine for postoperative analgesia was performed. Thirty minutes before the end of surgery, paracetamol 15 mg/kg was administered to group P, whereas the same volume of saline solution was delivered in group C. The neuromuscular block was reversed by neostigmine 0.05 mg/kg and atropine 0.015 mg/kg for extubation, and the patients were transferred to the recovery room.

Each patient received patient-controlled intravenous analgesia with meperidine (10-mg bolus, 20-minute lock out, no infusion dose, and 4-hour limit) for postoperative analgesia. All patients were to receive tenoxicam 20 mg intravenously as rescue analgesia when the visual analog scale (VAS) score was >3.

Each patient's age, sex, duration of surgery, kidney stone size, and nephrostomy tube size were recorded. CRBD was evaluated with a 4-point scale (1 = no discomfort; 2 = mild, revealed on questioning only; 3 = moderate, stated by the patient without being questioned; 4 = severe, urinary urgency demonstrated by behavioral responses such as attempts to remove the urinary catheter, restless extremity movements, verbal responses) 30 minutes and 1, 2, 4, 6, and 12 hours postoperatively.

Postoperative pain levels due to percutaneous tract and nephrostomy catheter were evaluated by the VAS score (0 = no pain, 10 = worst pain possible). Although pain management was aimed to be kept to VAS scores of ≤3, the analgesia level and total amount of delivered meperidine were recorded postoperatively at the same time points.

Sedation levels were assessed according to Ramsey Sedation Scale (1 = anxious and agitated, 2 = cooperative and calm; 3 = drowsy but responsive to commands, 4 = asleep but responsive to a glabellar tap, 5 = asleep with a sluggish response to tactile stimulation, 6 = asleep and no response), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and peripheral oxygen saturation (Spo_2) were assessed postoperatively at the same time points. Postoperative potential adverse effects such as bradycardia (HR <60/min), hypotension (SBP <90 mm Hg), respiratory depression (Spo_2 <90%), nausea, vomiting, and deep sedation were carefully monitored and recorded during the 24-hour postoperative period.

Patient and surgeon satisfaction was also assessed with a 4-point Likert scale (1 = very satisfied, 2 = somewhat satisfied, 3 = somewhat dissatisfied, 4 = very dissatisfied) at 24 hours after the surgery.

Sample size calculation was based on the initial pilot study. First, we started the study with 12 patients in each group who were not included in the study. The power was 80% in the sample size calculation. Using the data acquired from those patients, we observed a mean standardized effect of ~0.5 and a mean correlation of ~0.35 for the lower triangle of correlations obtained from repeated CRBD severity scores. According to an article by Rochon[9], we decided that 64 patients were required for the study.

Data analysis was performed using SPSS 18.0 (version 11.0, SPSS Inc, Chicago, Illinois). Categorical variables were expressed as numbers and percentages, whereas numerical variables were expressed as means (SDs) or as median and minimum-maximum values in come cases. The intergroup comparison of categorical variables was performed using the χ^2 test. The intergroup comparison of numerical variables was performed using a t test when the assumptions were fulfilled and the Mann-Whitney U test when the assumptions were not fulfilled. A repeated-measures ANOVA was used to compare the variances occurring over time in the same individuals. $P < 0.05$ was recognized as statistically significant.

RESULTS

Sixty-four patients scheduled for PNL were enrolled in the study. **Figure 1** presents the allocation of patients in groups. The groups were comparable with respect to demographic data, nephrostomy tube size, duration of surgery, and stone size (**Table I**).

The CRBD scores showed significant differences between the groups at all time points except the values at 12 hours (**Figure 2**). The number of patients who experienced moderate discomfort was significantly lower in group P compared with group C at 1, 2, 4, and 6 hours ($P < 0.05$). None of the patients in group P had severe CRBD at all time points except 1 patient at the 1 hour postoperatively (**Table II**).

Comparison of VAS scores showed that the scores were lower in group P than in group C when measurements were performed within the first 2 hours postoperatively. However, the difference between the groups was not statistically significant, and the following measurements revealed only minimal differences between the 2 groups in terms of VAS scores ($P > 0.05$) (**Table III**). Total consumption of meperidine was significantly higher in group C (group P: 52.72 [63.73] mg; group C: 75.81 [58.16] mg; $P = 0.018$), and no patients required rescue analgesia with tenoxicam.

Regarding the Ramsey Sedation Scale, the number of agitated and anxious patients was significantly higher in group C at 30 minutes and 1 hour ($P = 0.001$ and $P = 0.04$, respectively); however, all patients were observed to be calm and cooperative after 2 hours.

There were no significant intergroup or intragroup differences regarding HR, SBP, and DBP. None of the patients exhibited hypotension, hypertension, bradycardia, tachycardia, or excessive sedation. Patient satisfaction scores were 4.53 (0.51) in group

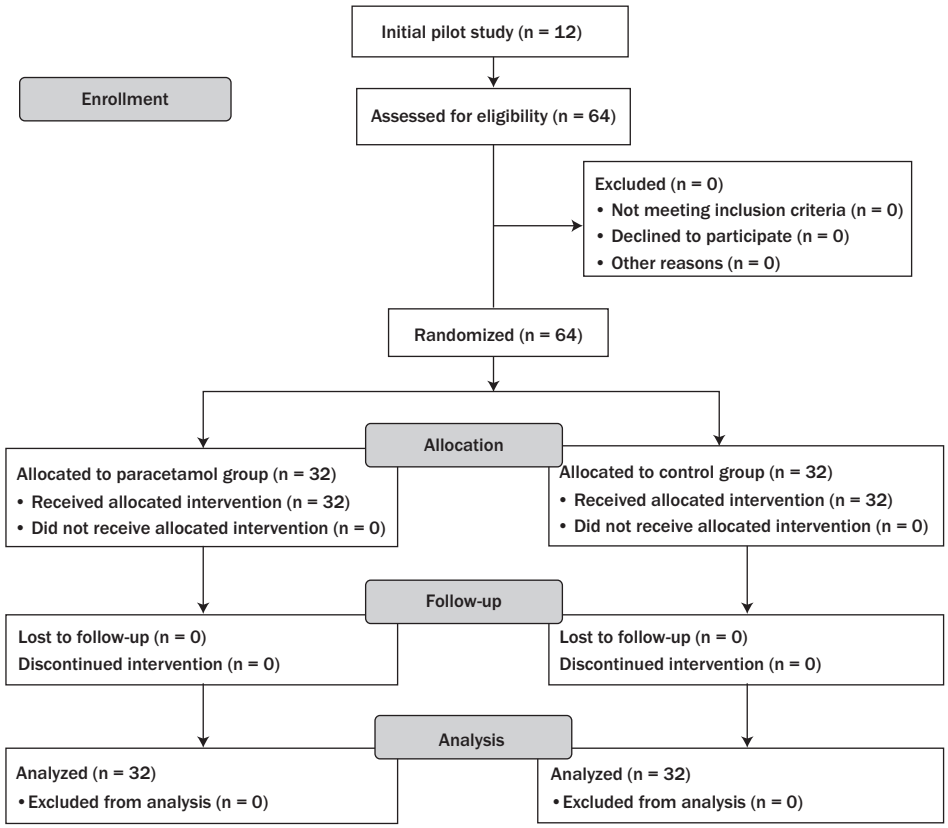

Figure 1. Study flow chart.

P and 3.84 (0.95) in group C. The results for patient satisfaction were significantly higher in group P ($P = 0.002$). Surgeon satisfaction scores were also significantly higher in group P (group P: 4.75 [0.44]; group C: 4.03 [0.82]; $P < 0.001$).

Table I. Demographic and surgical characteristics.

	Group P, Mean (SD)	Group C, Mean (SD)
Age, y	40.50 (12.72)	43.88 (12.75)
Height, m	168.03 (5.96)	166.19 (6.46)
Weight, kg	71.97 (12.42)	71.16 (10.53)
Duration of surgery, min	61.88 (31.82)	56.41 (25.44)
Renal stone size, cm^2	7.88 (4.12)	7.34 (3.98)
Nephrostomy catheter size, French	18.69 (0.97)	18.81 (1.00)

Data expressed as mean (SD).

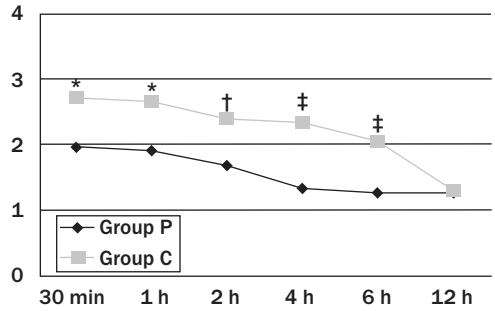

Figure 2. Severity of catheter-related bladder discomfort. Group C, control group; Group P, paracetamol group. *$P = 0.002$; †$P = 0.001$; ‡$P < 0.001$.

DISCUSSION

In this study, we evaluated the efficacy of paracetamol in patients who underwent PNL and urinary catheterization with regard to the clinical mechanisms of CRBD. We found that an intraoperative single dose of intravenous paracetamol decreases the severity of CRBD and meperidine consumption.

Urinary catheters inserted in the bladder for urologic surgeries may become a serious source of discomfort for patients. CRBD is an important entity that should be monitored to ensure patient satisfaction. Anesthesiologists must alleviate the stressful CRBD symptoms during the postoperative period to avoid a high incidence of CRBD. The clinical profile of CRBD, characterized by frequent and urgent need for urination, is very similar to that of OAB, which is characterized by urinary urgency with or without urge incontinence. Therefore, medications effective in treating OAB were also investigated in the management of CRBD.[2,4,6] Oxybutynin, an inhibitor of acetylcholine in smooth

Table II. Number of patients with catheter-related bladder discomfort.

	Time											
	30 min		1 h		2 h		4 h		6 h		12 h	
Discomfort	P	C	P	C	P	C	P	C	P	C	P	C
None, no.	10	4	12	5	13	7	20	7	23	10	24	22
Mild, no.	13	8	12	7	16	8	9	7	9	10	7	10
Moderate, no.	9	13	7*	14	3†	14	1‡	18	0‡	12	1	0
Severe, no.	0§	7	1*	6	0	3	0	0	0	0	0	0

C = control group (n = 32); P = paracetamol group (n = 32).
*$P = 0.018$.
†$P = 0.002$.
‡$P < 0.001$.
§$P = 0.009$.

Table III. VAS values of the groups.

VAS Score	Group P: Mean (SD), Median (Min-Max)	Group C: Mean (SD), Median (Min-Max)	*P*
30 min	2.19 (1.49), 3 (0–4)	2.94 (0.88), 3 (0–4)	0.055
1 h	1.84 (1.25), 2 (0–3)	2.41 (0.84), 2.5 (0–4)	0.119
2 h	2.06 (1.11), 2 (0–3)	2.19 (1.0), 2.5 (0–3)	0.609
4 h	1.97 (1.15), 2 (0–3)	2.09 (1.03), 2 (0–3)	0.783
6 h	1.88 (1.26), 2 (0–3)	1.91 (0.93), 2 (0–3)	0.520
12 h	1.63 (1.26), 2 (0–3)	1.53 (1.02), 2 (0–3)	0.453

Group C = control group; Group P = paracetamol group; Min-Max = minimum-maximum; VAS = visual analog scale.

muscles, and tolterodine, a competitive muscarinic acid, both of which are also used in OAB treatment, have been reported to achieve successful outcomes in relieving CRBD symptoms. However, these agents may initiate undesirable effects such as dry mouth, facial blushing, and blurry vision. Moreover, they are known to make no contribution to postoperative analgesia.[4,10] Gabapentin, an anticonvulsant drug, has also been studied in the treatment of CRBD symptoms because of its inhibitor activity on afferent C fibers by suppressing peripheral sensitization, which is similar to OAB.[6,11] However, the use of gabapentin for urologic dysfunction has been an off-label use and has no positive impact on postoperative pain. Ketamine, which binds with *N*-methyl-D-aspartate, muscarinic, and cholinergic receptors, has been shown to reduce the severity and incidence of CRBD. However, intravenous ketamine has been found to be associated with increased level of sedation despite the use of subhypnotic doses.[5]

Elevated urinary levels of PGE_2 in patients with OAB and lower urinary tract obstruction suggest that PGE_2 may play a role in these clinical entities.[12–14] PGs are produced in detrusor muscles and mucosa and play an important role in the regulation of lower urinary tract functions.[15] PG synthesis has been shown to be triggered by physiologic stimulations such as detrusor muscle contraction, damage in the bladder mucosa, nerve excitation, and activity of inflammation mediators such as bradykinin.[16] The mechanism of elevated PG synthesis during CRBD may be the increased activation of cyclooxygenase-2 (COX-2) enzyme, the inducible group of COX enzymes, with inflammatory stimulation due to the presence of the catheter. Thus, an elevated PGE_2 level may lead to the occurrence of CRBD with lower urinary tract symptoms such as urinary urgency, frequent urination, and urge incontinence.

Regarding the possible mechanism of CRBD, we hypothesized the use of paracetamol, which has been shown to inhibit PG synthesis in intact cells and act as a COX-2 inhibitor, would alleviate the occurrence and symptoms of CRBD.[17,18] Paracetamol has been commonly preferred for the management of postoperative pain and has the advantage of causing fewer adverse effects than nonsteroidal anti-inflammatory drugs and opioids.[19] Paracetamol has also been shown to significantly inhibit PGE_2 release from the dorsal horn of the spinal cord in rats.[20] Moreover, paracetamol has been shown to selectively suppress peripheral PGE_2 release in patients with acute inflammation after a brief surgical

intervention.[21] The intravenous form of paracetamol also provides an administration advantage during intraoperative general anesthesia practice.

In this study, CRBD was significantly less in patients who received paracetamol intraoperatively during PNL. This may be attributed to the assumption that intraoperative paracetamol delivery may have a therapeutic impact on CRBD. Pain scores were comparable in both groups; however, meperidine consumption was significantly higher in group C. This result may be interpreted as CRBD symptoms possibly aggravating the pain during the postoperative period.[22] However, the 23-mg difference in meperidine consumption between groups might be important for clinical management of patients with specific physical characteristics and postoperative needs for pain relief in clinics.

The patients in group P were less agitated and anxious in the early postoperative period. When compared with the other agents, also having sedative properties, used for CRBD treatment, the adequate level of recovery may be regarded as an advantage of intravenous paracetamol. Furthermore, patient and surgeon satisfaction assessments also favor paracetamol use for the management of CRBD.

The main limitation of this study was the possibility of misperception between CRBD and surgical symptoms such as pain and abdominal discomfort. In other words, surgery-related discomfort may blunt the accuracy of CRBD assessment. We believe that local anesthetic infiltration to the surgical site and effective postoperative pain management may relieve concerns about this issue.

In conclusion, we suggest that paracetamol is an effective drug in the management of CRBD.

ACKNOWLEDGMENTS

All authors contributed equally to the study design, data collection, data interpretation, figure creation, and writing of the manuscript.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Binhas M, Motamed C, Hawajri N, et al. Predictors of catheter-related bladder discomfort in the post-anaesthesia care unit. *Ann Fr Anesth Reanim*. 2011;30:122–125.
2. Agarwal A, Yadav G, Gupta D, et al. Evaluation of intra-operative tramadol for prevention of catheter-related bladder discomfort: a prospective, randomized, double-blind study. *Br J Anaesth*. 2008;101:506–510.
3. Antunes-Lopes T, Carvalho-Barros S, Cruz CD, et al. Biomarkers in overactive bladder: a new objective and noninvasive tool? *Adv Urol*. 2011;2011:382431.
4. Agarwal A, Dhiraaj S, Singhal V, et al. 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;96:377–380.
5. Agarwal A, Gupta D, Kumar M, et al. Ketamine for treatment of catheter related bladder discomfort: a prospective, randomized, placebo controlled and double blind study. *Br J Anaesth*. 2006;96:587–589.

6. Agarwal A, Dhiraaj S, Pawar S, et al. An evaluation of the efficacy of gabapentin for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study. *Anesth Analg*. 2007;105:1454–1457.
7. Smith HS. Perioperative intravenous acetaminophen and NSAIDs. *Pain Med*. 2011;12:961–981.
8. Mitchell JA, Akarasereenont P, Thiemermann C, et al. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. *Proc Natl Acad Sci U S A*. 1993;90:11693–11697.
9. Rochon J. Sample size calculations for two-group repeated-measures experiments. *Biometrics*. 1991;7:1383–1398.
10. Agarwal A, Raza M, Singhal 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;101:1065–1067.
11. Carbone A, Antonio C, Palleschi G, et al. Gabapentin treatment of neurogenic overactive bladder. *Clin Neuropharmacol*. 2006;29:206–214.
12. Kim JC, Park EY, Seo SI, et al. Nerve growth factor and prostaglandins in the urine of female patients with overactive bladder. *J Urol*. 2006;175:1773–1776.
13. Kim JC, Park EY, Hong SH, et al. Changes of urinary nerve growth factor and prostaglandins in male patients with overactive bladder symptom. *Int J Urol*. 2005;12:875–880.
14. Aoki K, Hirayama A, Tanaka N, et al. A higher level of prostaglandin E2 in the urinary bladder in young boys and boys with lower urinary tract obstruction. *Biomed Res*. 2009;30:343–347.
15. Andersson KE. Detrusor myocyte activity and afferent signaling. *Neurourol Urodyn*. 2010;29: 97–106.
16. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev*. 2004;84:935–986.
17. Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Ther*. 2005;12:46–55.
18. Bonnefont J, Courade JP, Alloui A, et al. Antinociceptive mechanism of action of paracetamol [in French]. *Drugs*. 2003;63 Spec No 2:1–4.
19. Jahr JS, Lee VK. Intravenous acetaminophen. *Anesthesiol Clin*. 2010;28:619–645.
20. Muth-Selbach US, Tegeder I, Brune K, et al. Acetaminophen inhibits spinal prostaglandin E2 release after peripheral noxious stimulation. *Anesthesiology*. 1999;91:231–239.
21. Lee YS, Kim H, Brahim JS, et al. Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. *Pain*. 2007;129:279–286.
22. Tauzin-Fin P, Sesay M, Svartz L, et al. Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy. *Br J Anaesth*. 2007;99:572–575.

Address correspondence to: Pinar Ergenoglu, MD, Anesthesiology and Reanimation Department, Baskent University School of Medicine, 39. Sk. No. 6, 01250 Adana, Turkey. E-mail: pergenoglu@yahoo.com