

# The effect of intravenous preemptive paracetamol on postoperative fentanyl consumption in patients undergoing open nephrectomy: A prospective randomized study

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## Abstract

**Aim:** We investigated the efficacy of intravenous (IV) preemptive paracetamol on postoperative total fentanyl consumption and fentanyl-related side effects in patients undergoing open nephrectomy.

**Materials and Methods:** A total of 60 patients scheduled for elective open nephrectomy under general anesthesia were included. All patients received Patient-controlled IV analgesia with fentanyl postoperatively. Patients were randomly allocated into three equal groups: The fentanyl group received 100 mL of IV normal saline as a placebo, with the first dose ending 30 min before intubation. In paracetamol group, IV 1 g paracetamol was given to the patients 30 min after extubation with repeated doses every 6 h totally 4 times a day. In preemptive paracetamol group, patients received IV 1 g paracetamol every 6 h, with the first dose ending 30 min before intubation.

**Results:** Postoperative cumulative fentanyl consumption for 24 h was significantly higher in the fentanyl group ( $1009 \pm 139.361 \mu\text{g}$ ) than those of paracetamol ( $752.25 \pm 112.665 \mu\text{g}$ ) and preemptive paracetamol groups ( $761.10 \pm 226.625 \mu\text{g}$ ) ( $P = 0.001$  for both). In early postoperative period (0-4 h); whereas total fentanyl consumption showed no statistically significant difference among groups ( $P = 0.186$ ), the nausea-vomiting scores were significantly higher in the fentanyl group compared with other groups ( $P = 0.012$ ).

**Conclusion:** In patients undergoing open nephrectomy, use of preemptive or postoperative paracetamol reduces fentanyl related nausea-vomiting without a decrease in total fentanyl consumption in the early postoperative period. Furthermore, use of preemptive or postoperative paracetamol reduces total fentanyl requirements in the first 24 h postoperatively providing a safe and effective postoperative analgesia.

**Key words:** Fentanyl, intravenous paracetamol, open nephrectomy, preemptive analgesia

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## Introduction

After renal operations patients experience incisional pain, as a result, of excess muscle cutting. Inadequate postoperative pain management extends the duration of hospital stay and may lead to undesirable adverse effects such as respiratory

insufficiency and thromboembolic complications.<sup>[1]</sup> With the changes in healthcare dictated by economic pressures, there are significant efforts to reduce the patient's length of hospital stay without comprising the quality of patient care.<sup>[2]</sup>

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The preemptive concept involves administering an analgesic agent before the onset of the painful stimulus, thus, it may reduce or abolish the development of pain hypersensitization, resulting in less post-stimulus pain.<sup>[3,4]</sup> It was shown that preemptive analgesia provides a reduction in perioperative stress, shortening length of hospital stay, reduction in hospital costs, an improvement in patient satisfaction and a reduction in postoperative morbidity.<sup>[3,4]</sup> Opioids are the first-choice medications for the postoperative pain management.<sup>[5]</sup> Patient-controlled intravenous analgesia (PCIA) is commonly used for the administration of opioids in the postoperative period.<sup>[6]</sup> However, opioids have significant side effects such as respiratory depression, excessive sedation, ileus, nausea, and vomiting. Therefore, provision of a reduction in the dose of opioid used is essential for reducing opioid-related side effects.<sup>[1]</sup> It has been reported that the addition of paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs) provides preemptive analgesia that decreases postoperative opioid dose requirements and reduces opioid-related adverse effects.<sup>[7]</sup> Paracetamol has a well-established safety and analgesic profile, and it rapidly passes the blood brain-barrier. It is known that paracetamol reaches a high concentration in the central nervous system. It appears to exert its analgesic effect by inhibiting the cyclooxygenase enzyme and through the serotonergic system. However, the mechanism of the analgesic action of paracetamol is still poorly defined.<sup>[7,8]</sup>

We designed a prospective randomized study to investigate the efficacy of intravenous (IV) preemptive paracetamol (Perfalgan<sup>®</sup>, Bristol-Myers Squibb, France) on postoperative pain scores, patient satisfaction, total fentanyl consumption and the incidence of fentanyl-related side effects in patients undergoing open nephrectomy.

## Materials and Methods

After the study had been approved by the Ethics Committee of Ataturk University Research Ethics Committee, Erzurum, Turkey, this study was performed over a 10-month period in Department of Anesthesiology and Reanimation of Ataturk University, Medical Faculty. Written informed consent was obtained from all participating patients and the Helsinki Declaration was respected all over the study course. Patients between the ages of 18 and 70 years, American Society of Anesthesiologists (the classification of the ASA) physical status I-II, who underwent elective nephrectomy with laparotomy were included. Patients with a history of allergy to any of the study medications (opioid, general anesthetic agents or paracetamol), history of opioid use, hepatic or renal disease, additional co-morbid disease such as diabetes mellitus, hypertension, psychosis and use of antiemetic, antihistaminic, analgesic or corticosteroid 24 h prior to surgery and were unable to use PCIA device were excluded from the study.

All patients were randomly divided into three groups by closed envelope method. All patients received PCIA with fentanyl postoperatively. The fentanyl group received IV normal saline (every 6 h totally 4 times a day) as a placebo, with the first dose ending 30 min before intubation. In paracetamol group, IV 1 g paracetamol was given to the patients 30 min after extubation with repeated doses every 6 h totally 4 times a day. In preemptive paracetamol group, IV 1 g paracetamol (every 6 h totally 4 times a day) was given to the patients, with the first dose ending 30 min before intubation. Patients' age, weight, height, duration of anesthesia (the time from anesthesia induction to the completion of surgery) and duration of operation (the time from the start of the surgical incision to the completion of surgery) were recorded. Patients' systolic and diastolic blood pressures, respiratory and heart rates at 4, 8, 12, and 24 h and fentanyl consumption at 4, 12, 24 h postoperatively were recorded. The presence of respiratory depression (a rate below 12 breaths per minute), bradycardia (heart rate below 50 bpm) and hypotension (a decrease of >30% in mean arterial pressure) were also recorded. In the case of hypotension, IV bolus infusion of 500 ml Ringer's lactate and ephedrine IV, 5 mg were used. Bradycardia was treated using atropine sulfate (IV, 0.5 mg).

Preoperatively, all patients were informed about visual analogue scale (VAS), and the use of the PCIA device (Abbott Pain Management Provider, North Chicago, IL) and Ringer's lactate 500 ml IV bolus infusion was given for hydration. All patients enrolled in the study received a standardized general anesthesia regimen. After standard monitoring including non-invasive arterial pressure, electrocardiography, and pulse oximetry was established in the operating room, preoxygenation with 100% oxygen for 3 min was provided for all patients. Later, anesthesia was induced with propofol 2 mg/kg and muscle relaxation was provided with rocuronium bromide 0.6 mg/kg. Anesthesia was maintained with 65% nitrous oxide in oxygen and sevoflurane 1-1.5% at end-tidal carbon dioxide between 30 and 35 mmHg. None of the patients received an opioid before and during operation. At the end of the surgery, tracheal extubation was provided after neuromuscular blockade was reversed using neostigmine 0.04 mg/kg and atropine 0.02 mg/kg. In the post-anesthesia recovery room, all patients received IV analgesia via a PCIA containing fentanyl 1.5 µg/kg loading dose. PCIA device was set as a bolus dose of 25 µg; with a lock-out time of 10 min; and 400 µg total infusion dose with a 4-h limitation. Continuous infusion of fentanyl was not administered to the patients. Both patients and anesthesiologist were blinded to treatment groups in the post-anesthesia recovery room.

Postoperative pain at rest was evaluated using a standard 10 cm VAS (0 cm = no pain, 10 cm = worst pain imaginable) at 2, 4, 8, 12, and 24 h postoperatively. Status of patient satisfaction was scored at 24 h

postoperatively (1 = very dissatisfied, 2 = dissatisfied, 3 = satisfied, 4 = very satisfied) and the results were recorded.

No patients received anti-emetic medication prophylactically. Nausea and vomiting were evaluated on a three-point ordinal scale (0 = none, 1 = nausea and 2 = vomiting) at 0-4 and 4-24 h after operation. Vomiting was treated with metoclopramide 10 mg IV, as necessary. Postoperative sedation was objectively graded by the anesthetist for 4 and 12 h using a four-point scale: 1 = awake, 2 = drowsy, 3 = asleep, can be easily roused, and 4 = fast asleep and recorded.

Statistical analysis was performed using SPSS for Windows (version 15.0) statistical package (SPSS Inc., Chicago, IL, USA). Patient characteristics such as age, weight, VAS score, fentanyl consumption, sedation scores, and frequency of side effects were analyzed using one-way ANOVA test. The Chi-Square test was used for comparison of hourly values of the scores. Russ Lenth's Power and sample size calculation application A was used for power analysis of this study.<sup>[9]</sup> The primary endpoint of the study was to evaluate 30% or more decrease in fentanyl consumption among the groups at estimated time intervals postoperatively. Nineteen patients in each group were needed to detect the difference with a power of 80% at 5% significance level.

## Results

Seventy patients met the inclusion criteria for the study. However, five patients refused to participate in the study, and five patients did not meet the inclusion criteria. Eventually, the study population consisted of sixty patients ( $n = 20$ , for each group) [Figure 1].<sup>[10]</sup> The baseline patients' characteristics and operation times of each group are as shown in Table 1. There was no statistically significant difference among the groups regarding sex, age, weight, duration of anesthesia,

and operation ( $P > 0.05$ ). No differences were found among the groups in terms of cardiorespiratory variables such as systolic and diastolic blood pressure, heart rate and oxygen saturation in the postoperative period. Respiratory depression, bradycardia and hypotension were not observed in any patient. The fentanyl consumption of the groups at 4, 12 and 24 h postoperatively is shown Figures 2a-c. Fentanyl consumption in the 4<sup>th</sup> h postoperative period showed no statistically significant difference among the groups ( $P = 0.186$ ) [Figure 2a]. In terms of total fentanyl consumption at 12 h postoperatively, fentanyl group had significantly higher total fentanyl consumption than those of paracetamol group and preemptive paracetamol group ( $716.60 \pm 101.38 \mu\text{g}$ ,  $566.00 \pm 123.92 \mu\text{g}$ ,  $561.10 \pm 176.593 \mu\text{g}$ , respectively (for both groups,  $P = 0.01$ ) [Figure 2b]. Furthermore, cumulative fentanyl doses for 24 h postoperatively were found higher in the fentanyl group compared with the paracetamol and preemptive paracetamol groups ( $1009 \pm 139.361 \mu\text{g}$ ,  $752.25 \pm 112,665 \mu\text{g}$ ,  $761.10 \pm 226.625 \mu\text{g}$ , respectively (for both groups,  $P = 0.01$ ) [Figure 2c].

Nausea and vomiting scores in the early postoperative period (0-4 h) were found to be higher in the fentanyl group than those of the paracetamol group and preemptive paracetamol group ( $P = 0.012$ ) [Table 2]. However, late

**Table 2: The nausea and vomiting scores at the first postoperative 24 h in groups**

Postoperative period	Score	Group (n=20 (%))		
		Fentanyl	Paracetamol	Preemptive paracetamol
Early postoperative period (0-4 h)	0	8 (40)	9 (45)	14 (70)
	1	5 (25)	9 (45)	5 (25)
	2	7 (35)	2 (10)	1 (5)
Late postoperative period (4-24 h)	0	13 (65)	15 (75)	11 (55)
	1	4 (20)	2 (10)	7 (35)
	2	3 (15)	3 (15)	2 (10)

Results are given as n (%)

**Table 1: Demographic and surgical characteristics of patients**

Characteristics of patients	Group (n=20)			P values
	Fentanyl	Paracetamol	Preemptive paracetamol	
Sex (male/female)	9/11	12/8	12/8	0.818
Age (years)	44.30±16.86	45.20±13.80	53.80±12.62	0.920
Weight (kg)	70.00±11.81	71.50±9.33	72.85±10.33	0.756
Height (cm)	168.5±6.22	169.4±6.81	169.7±6.91	0.820
Duration of anesthesia (min)	151.15±70.01	159.75±57.50	158.00±31.01	0.698
Duration of operation (min)	134.00±60.86	135.25±55.57	131.25±28.97	0.388
SBP (mmHg)	117.10±15.17	117.90±15.25	117.75±14.76	0.991
DBP (mmHg)	73.15±12.43	73.70±11.37	73.50±11.53	0.989
MAP (mmHg)	84.70±21.21	88.00±11.62	88.30±11.96	0.746
HR (bpm)	80.30±12.34	79.20±13.07	84.10±13.80	0.559

Values are means±SD or number of patients (n). SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MAP=Mean arterial pressure; HR=Heart rate; ASA=American Society of Anesthesiologists; SD=Standard deviation

postoperative period nausea and vomiting scores did not differ among groups ( $P = 0.537$ ) [Table 2]. There was no difference among groups in terms of the incidence of pruritus ( $P = 0.765$ ). Similar sedation scores were found among groups [Table 3].

**Table 3: Postoperative sedation scores of patients at the 4<sup>th</sup> h and 12<sup>th</sup> h**

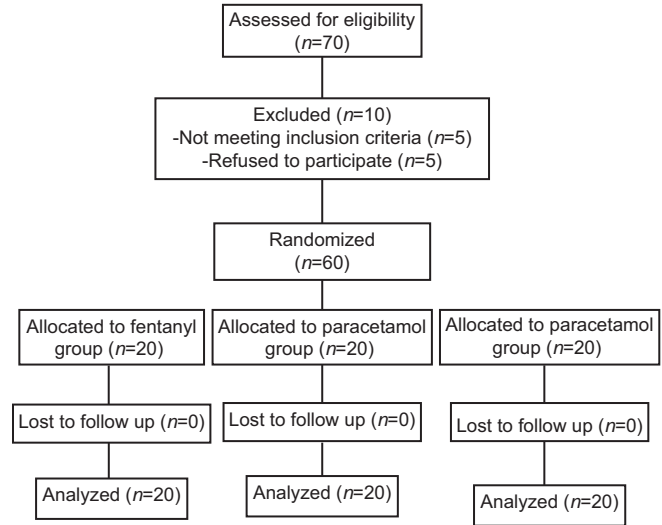
Postoperative period	Score	Group (n=20) (%)		
		Fentanyl	Paracetamol	Preemptive paracetamol
Postoperative 4 <sup>th</sup> h	1	11 (55)	18 (90)	15 (75)
	2	8 (40)	2 (10)	5 (25)
	3	1 (5)	0 (0)	0 (0)
Postoperative 12 <sup>th</sup> h	1	19 (95)	17 (85)	20 (0)
	2	1 (5)	3 (15)	0 (0)

**Table 4: The patient satisfaction status in groups**

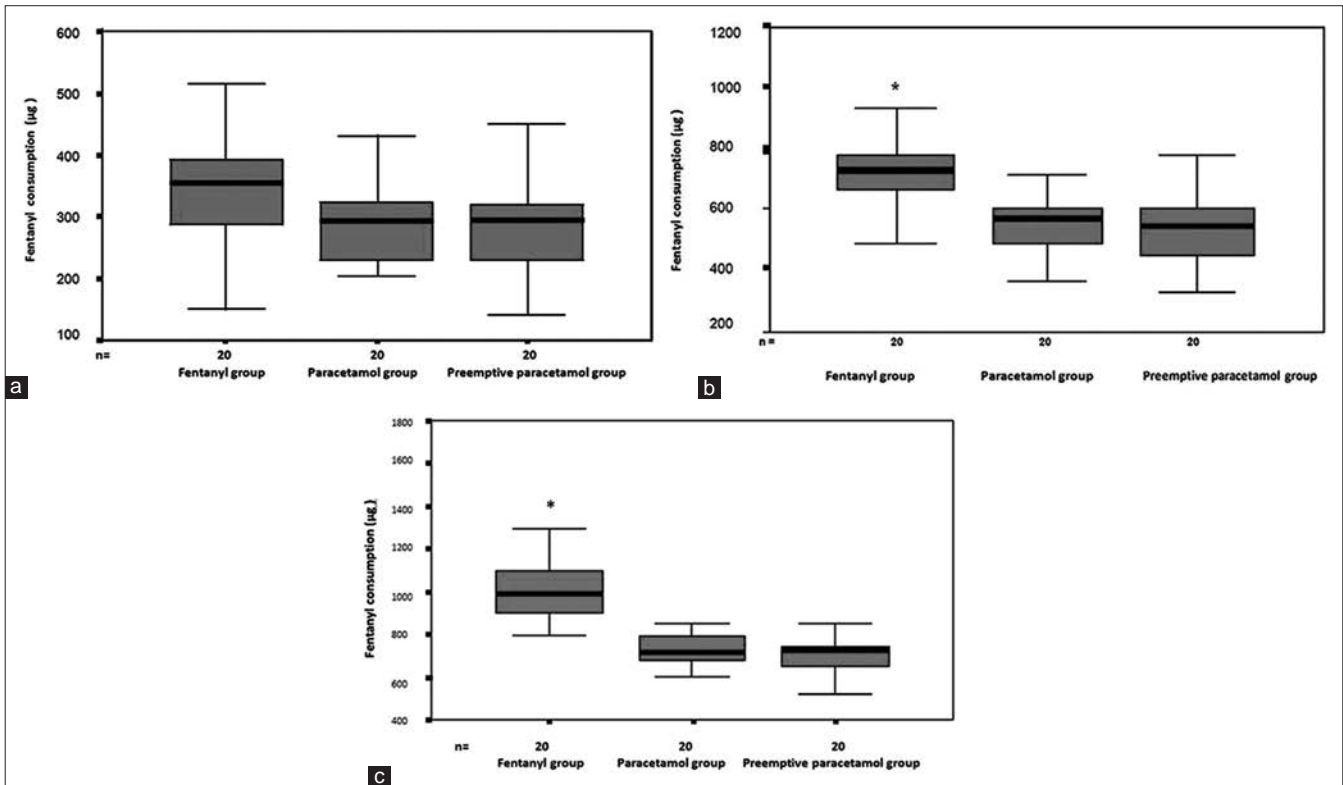
Patient satisfaction status	Group (n=20) (%)		
	Fentanyl	Paracetamol	Preemptive paracetamol
Dissatisfied	0 (0)	1 (5)	1 (5)
Satisfied	10 (50)	7 (35)	12 (60)
Very satisfied	10 (50)	12 (60)	7 (35)

Results are given as n (%)

Median values of VAS scores at rest in the first 24 h postoperatively were  $3.9 \pm 1.4$  in the fentanyl group,  $4.1 \pm 1.3$  in the paracetamol group and  $3.8 \pm 1.6$  in preemptive paracetamol group and these values were not statistically different among groups ( $P > 0.05$ ). There was no statistically significant difference among groups in terms of patient satisfaction ( $P > 0.05$ ) [Table 4].



**Figure 1:** Consort flow diagram. The course of patients through this study was shown



**Figure 2:** (a) Total fentanyl consumption in groups in the first 4 h postoperatively, (b) Total fentanyl consumption in groups in the first 12 h postoperatively. (\* $P = 0.01$ , compared with other groups), (c) Total fentanyl consumption in groups in the first 24 h postoperatively. (\* $P = 0.01$ , compared with other groups)

## Discussion

In the present study, the effect of preemptive IV paracetamol administration on the postoperative fentanyl requirement was investigated in patients undergoing open nephrectomy. We found that the use of IV paracetamol as preemptive analgesic agent reduced the total amount of the fentanyl requirement in the first 24 h after surgery, and it was an effective and safe method for postoperative pain control in open nephrectomy cases. Furthermore, the administration of preemptive IV paracetamol decreased the incidence of nausea and vomiting in the early postoperative period, while this decrease was not observed in the late postoperative period. However, there were no differences between preemptive and postoperative paracetamol administration in terms of postoperative analgesia quality and total fentanyl consumption.

The preemptive concept involves administering an analgesic agent before the onset of a painful stimulus and provides sufficient postoperative pain control and a decrease in the postoperative total analgesic consumption.<sup>[11,12]</sup> Opioid analgesics and/or NSAIDs are commonly used in the treatment of moderate to severe postoperative pain, especially in the early period. However, opioid-related side-effects and gastrointestinal side-effects may occur depending on the use of these drugs. Use of non-opioid analgesics in the pre-emptive period is recommended to reduce the postoperative opioid requirement.<sup>[2]</sup> Fentanyl was preferred in this current study, because fentanyl dissolves better in oil than morphine, and, therefore, the onset of its analgesic action is faster, and it has fewer side effects than morphine.<sup>[2]</sup>

There are studies in the literature on the effect of IV paracetamol on analgesic requirement during surgery or postoperative period following different surgical procedures.<sup>[13-16]</sup> It was reported that combined use of IV paracetamol with morphine decreases the postoperative morphine requirement by 46% and increases patient satisfaction in patients undergoing hip arthroplasty.<sup>[3]</sup> Similarly, Delbos and Boccard<sup>[14]</sup> also reported a 24% decrease in the postoperative morphine requirement in patients undergoing knee ligamentoplasty when IV paracetamol was given every 6 h in addition to morphine. In another study,<sup>[15]</sup> a significant decrease was demonstrated in cumulative doses of morphine in patients receiving IV injection of 2 g propacetamol (every 6 h for 3 days) in addition to PCIA morphine after spinal fusion surgery. Kiliçaslan *et al.*<sup>[17]</sup> investigated the effects of the iv paracetamol combined with PCIA (using tramadol) on postoperative tramadol consumption for post-caesarean pain control. They reported that paracetamol produces effective analgesia and reduces postoperative tramadol consumption. Consistent with the above studies, the use of preemptive

or postoperative paracetamol reduced the postoperative fentanyl requirement by an average of 20% in this study.

The use of preemptive doses of paracetamol provided successful postoperative pain management following different surgeries.<sup>[7,12,18,19]</sup> However, this study is the first researching the effect of preemptive paracetamol on the postoperative fentanyl requirement in patients undergoing open nephrectomy. Some studies concluded that using paracetamol as a preemptive analgesic agent is no more effective than other drugs.<sup>[12,19]</sup> However, paracetamol was used in very low doses (500 mg and 320 mg) in these studies compared with this present study (1 g). In fact, Juhl *et al.*<sup>[20]</sup> demonstrated that IV 2 g paracetamol has more effective analgesic effects than IV 1 g paracetamol. IV paracetamol for postoperative pain control in children is also used in an efficient and reliable manner.<sup>[21]</sup> In a meta-analysis,<sup>[22]</sup> patients receiving propacetamol or paracetamol needed 30% less opioid over 4 h and 16% less opioid over 6 h than those receiving placebo postoperatively. In this current study, an effective postoperative analgesia with decreased postoperative fentanyl consumption was found with the administration of preemptive IV paracetamol in nephrectomy cases.

Visual analogue scale scores at rest and patient satisfaction were similar among groups in this current study. Similar to our results, Alhashemi *et al.*<sup>[23]</sup> reported similar VAS scores and patient satisfaction in patients received IV acetaminophen combined with PCIA morphine compared with patients who received oral ibuprofen combined with PCIA morphine. Furthermore, Khalili *et al.*<sup>[12]</sup> compared postoperative pain scores and patient satisfaction in patients who received acetaminophen preoperatively or prior to skin closure following lower extremity orthopedic surgery, and they found no significant differences between groups.

Despite its widespread use in various clinical conditions, the mechanism of the analgesic action of paracetamol is still not fully elucidated. Paracetamol has both a central inhibitor action on cyclooxygenase and an interaction with the serotonergic system.<sup>[24,25]</sup> In addition, its weak effect on the peripheral system has recently been demonstrated.<sup>[8]</sup> NSAIDs and opioids have several side effects such as postoperative nausea and vomiting (PONV), drowsiness, respiratory depression, gastrointestinal adverse effects and bladder dysfunction. PONV is one of the most undesirable postoperative outcomes for the patients. Furthermore, PONV leads to a delay in oral intake and duration recovery and be discharged from the hospital. Paracetamol has less side-effect profile for postoperative pain control, so it is preferred to avoid opioid and NSAIDs related side effects.<sup>[2]</sup> Hepatotoxicity is the most feared side

effect depending on the use of paracetamol. Therefore, it is recommended that paracetamol (1 g IV) should be applied with an interval of 6 h and used not exceeding 4 g/day for postoperative analgesia.<sup>[24]</sup> The daily dose of paracetamol in this current study did not exceed 4 g.

In our study, the incidence of nausea and vomiting in the early postoperative period was found to be lower in patients who received preemptive or postoperative paracetamol than in patients who received no paracetamol. Moreover, fentanyl consumption in the early postoperative period was not different among groups. These results suggest that the first dose of paracetamol may create an antiemetic effect. Serotonin antagonists act in the vomiting center and are used to treat nausea and vomiting in clinics; and paracetamol affects the central serotonergic system. IV paracetamol achieves peak plasma levels crossing the blood-brain barrier within 30 min after administration.<sup>[24]</sup> Paracetamol may decrease the incidence of nausea and vomiting by affecting some of the serotonergic pathways in the central nervous system. Indeed, intraoperative administration of IV paracetamol decreased the incidence of PONV during the first 24 hours in children after strabismus surgery in Cok *et al.*'s<sup>[26]</sup> study. Furthermore, in a systematic review and meta-analysis,<sup>[27]</sup> it was reported that prophylactically administered IV acetaminophen for postsurgical pain reduces PONV. These results are consistent with our results.

There are several limitations in the present study. First, we did not assess VAS scores on activity. Second, we have studied a relatively small population. Studies with a larger sample need to be done to evaluate the effect of preemptive paracetamol on the quality of postoperative analgesia.

## Conclusion

In patients undergoing open nephrectomy, the use of preemptive or postoperative paracetamol reduces fentanyl related nausea-vomiting without a decrease in PCIA fentanyl consumption in the early postoperative period. Furthermore, preemptive or postoperative paracetamol reduces total fentanyl requirements in the first 24 h postoperatively providing a safe and effective postoperative analgesia with good patient satisfaction. However, the use of paracetamol preemptively had no advantage compared with the use of paracetamol postoperatively in terms of postoperative analgesia quality and total fentanyl consumption. The use of preemptive or postoperative IV paracetamol with postoperative PCIA fentanyl may provide a significant contribution to the multimodal methods of post-operative pain control.

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