



A Comparative Study of the Efficacy of IV Dexketoprofen, Lornoxicam, and Diclophenac Sodium on Postoperative Analgesia and Tramadol Consumption in Patients Receiving Patient-Controlled Tramadol

Hasta Kontrollü Tramadol Alan Hastalarda Deksketoprofen, Lornoksikam ve Diklofenak Sodyumun Postoperatif Analjezi ve Tramadol Tüketimi Üzerine Etkilerinin Karşılaştırılması

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Objective: This study was designed to compare the effects of dexketoprofen, lornoxicam, and diclophenac sodium on postoperative analgesia and tramadol consumption in patients receiving postoperative patient-controlled tramadol after a major abdominal surgery.

Methods: Eighty patients were randomized to receive one of the four study drugs. Patients in group dexketoprofen (DT) received IV 50 mg dexketoprofen, group lornoxicam (LR) received IV 8 mg lornoxicam, group diclophenac sodium (DS) received 75 mg IV diclophenac sodium and group saline (S) received 0.9% saline in 2 mL syringes, 20 min before the end of anaesthesia. A standardized (1 mg kg⁻¹) dose of tramadol was routinely administered to all patients as the loading dose at the end of surgery. Postoperatively, whenever patients requested, they were allowed to use a tramadol patient-controlled analgesia device giving a bolus dose (0.2 mg kg⁻¹) of tramadol. Pain, discomfort, and sedation scores, cumulative tramadol consumption, supplemental meperidine requirement, and side effects were recorded.

Results: Visual rating scale and patient discomfort scores were significantly lower in DT, LR and DS groups compared to those in in group S (p<0.001). Cumulative tramadol consumption was significantly lower in non-steroidal anti-inflammatory drug (NSAID)-treated groups at each study period after the second postoperative hour than in group S (p<0.001). Supplemental meperidine requirement was significantly higher in group S at each study period after postoperative 30 min than in NSAID-treated groups (p<0.01).

Conclusion: After major abdominal surgery, adding IV diclophenac, lornoxicam or dexketoprofen to patient-controlled tramadol resulted in lower pain scores, smaller tramadol consumption, less rescue supplemental analgesic requirement, and fewer side effects compared with the tramadol alone group.

Keywords: Dexketoprofen trometamol, diclophenac sodium, lornoxicam, patient controlled analgesia, tramadol

Amaç: Çalışmamızda büyük abdominal cerrahi sonrası deksketoprofen, lornoksikam ve diklofenak sodyumun postoperatif analjezi ve tramadol tüketimi üzerine etkilerinin karşılaştırılmasını amaçladık.

Yöntemler: Çalışmaya dahil ettiğimiz 80 hastayı randomize olarak dört gruba ayırdık. Anestezinin sonlandırılmasından 20 dakika önce hastalara grup deksketoprofende (DT) deksketoprofen 50 mg IV, grup lornoksikamda (LR) lornoksikam 8 mg IV, grup diklofenak sodyumda (DS) diklofenak sodyum 75 mg IV ve grup salinde (S) %0,9 salin 2 mL IV uyguladık. Cerrahinin bitiminde yükleme dozu olarak tüm hastalara tramadol 1 mg kg⁻¹ IV uyguladık. Postoperatif dönemde tüm hastalara 0,2 mg kg⁻¹ bolus dozunda tramadol verecek olan hasta kontrollü analjezi cihazı kurduk. Ağrı, hasta konforu ve sedasyon skorları, toplam tramadol tüketimi, ek analjezik meperidin gereksinimi ve yan etkileri kaydedtik.

Bulgular: Görsel derecelendirme skalası (visual rating scale; VRS) ve hasta konforu skorları grup S ile karşılaştırıldığında grup DT, LR ve DS'de belirgin olarak düşüktü (p<0,001). Toplam tramadol tüketimi postoperatif 2. saatten itibaren tüm çalışma zamanlarında nonsteroid antiinflamatuar ilaç (NSAİİ) gruplarında grup S'e göre belirgin olarak düşüktü (p<0,001). Ek analjezik meperidin gereksinimi postoperatif 30. dakikadan sonra tüm çalışma zamanlarında grup S'de NSAİİ gruplarına göre belirgin yüksekti (p<0,01).

Sonuç: Büyük abdominal cerrahi sonrası hasta kontrollü tramadol uygulamasına iv diklofenak, lornoksikam ve deksketoprofen eklenmesi, yalnız tramadol kullanımına göre daha düşük ağrı skorları, daha az tramadol tüketimi, ek analjezik gereksinimi ve yan etki sağlamaktadır.

Anahtar Kelimeler: Deksketoprofen trometamol, diklofenak sodyum, hasta kontrollü analjezi, lornoksikam, tramadol

Introduction

A synthetic mu-opioid agonist, tramadol hydrochloride, is one of the most commonly used analgesics for the management of postoperative pain. However, it has a limited analgesic potency and untoward side effects, such as nausea, vomiting, and constipation, particularly when used in high doses (1, 2).

Non-steroidal anti-inflammatory drugs (NSAIDs) alone or in combination with opioids have been proposed for the management of postoperative pain as a part of a multimodal analgesic regimen (3, 4). Several multimodal approaches have been advocated based on different combinations of anti-inflammatory drugs or paracetamol with tramadol (5). Although each agent has been demonstrated as being effective in reducing postoperative pain, supporting studies remain limited.

We hypothesized that in patients undergoing major abdominal surgery, adding intravenous (IV) lornoxicam, dexketoprofen, or diclophenac sodium to IV tramadol patient-controlled analgesia (PCA) would provide a better postoperative analgesia, lower tramadol consumption, and lesser side effects compared with tramadol PCA alone.

This prospective, randomized, double-blind, controlled study was designed to compare the effects of dexketoprofen, lornoxicam, and diclophenac sodium on postoperative analgesia and tramadol consumption in patients receiving postoperative patient-controlled tramadol after major abdominal surgery.

Methods

This study was approved by the Ethics Committee of the Ministry of Health of Turkey Clinical Drug Research, and the patients provided informed consent. We recruited 80 patients with American Society of Anesthesiologists physical status I or II patients, between the ages of 18-70, scheduled for a major abdominal surgery with general anaesthesia. Exclusion criteria included inability to use the patient-controlled analgesia PCA device, long-term use of opioid medications, history of hepatic, renal, cardiovascular or endocrine disease, and a history of chronic pain.

Patients were admitted to the preoperative unit 30 min before the operation. A cannula (18 gauges) was intravenously placed and 0.9% of saline infusion was started at a 10 mL kg⁻¹ h⁻¹ rate for hydration.

All patients were monitored with non-invasive blood pressure, electrocardiogram, end-tidal carbon dioxide, and peripheral oxygen saturation (Draeger-Primus Anaesthesia Device Monitor, Draeger Medical Systems, Inc 16 Electronics Avenue, Denver, MA 01923 USA) in the operating room before anaesthesia induction.

Anaesthesia was induced with IV thiopental sodium (4-5 mg kg⁻¹) and maintained with 1%-2% sevoflurane in a mixture

of 65% nitrous oxide and 35% oxygen with a total gas flow rate of 6 L min⁻¹. Neuromuscular relaxation was induced with IV vecuronium bromide (0.1 mg kg⁻¹) and maintained (0.03 mg kg⁻¹) by bolus administration of vecuronium.

At the beginning of the closure of peritoneum, patients were randomized to receive one of the four study drugs to be used 20 min before the termination of anaesthesia. Randomization was consecutively performed. The drugs were prepared by an anaesthetist, who was not one of the observers, in four 2 mL syringes, which contained dexketoprofen trometamol (50 mg) (Arvels 50 mg 2 mL amp, Ufsa İlaç Sanayi and Ticaret A.Ş., Istanbul, Turkey), lornoxicam (8 mg) (Xefo 8 mg 2 mL flacon, Nycomed İlaç Sanayi and Tic. Ltd. Şti., Istanbul, Turkey), diclophenac sodium (75 mg) (Diclofenac Injection 75 mg 3 mL amp, Astrapin Pharma, Pfaffen-Schwabenheim, Germany), or 0.9% saline per syringe. They were marked with a coded label to ensure the double-blind nature of the study.

Thus, patients in group DT (n=20) received IV 50 mg dexketoprofen trometamol. Group LR (n=20) received IV 8 mg lornoxicam, group DS (n=20) received 75 mg of IV diclophenac sodium, and group S (n=20) received 0.9% saline in 2 mL syringes 20 min before the termination of anaesthesia. These drugs were repeated three times a day to sustain postoperative analgesia during the first 24 h in groups.

At the closure of peritoneum, a standardized (1 mg kg⁻¹) dose of tramadol (Tramadolor 100 mg amp, Sandoz İlaç San. and Tic. A.Ş., Istanbul, Turkey) was administered to all patients as the loading dose. At the end of the surgery, residual neuromuscular block was antagonized with neostigmine (0.05 mg kg⁻¹) and atropine (0.015 mg kg⁻¹) combination and patients were then extubated. No other analgesic was intraoperatively administered except the study drugs according to the study procedure.

After extubation, patients were taken to the postoperative care unit; they were followed-up for 60 min. After total recovery from anaesthesia (as judged by the obey to command, grip a finger, ability to open the eyes and breathe deeply on request), whenever patients requested, they were allowed to use a tramadol PCA device (CADD Legacy PCA pump, Smiths Medical MD, Inc. St. Paul, MN, USA) giving a bolus dose of tramadol. The settings were IV tramadol, bolus dose of 0.2 mg kg⁻¹, with a lock-out time of 12 min and no background infusion. An anaesthetist determined the PCA settings.

Whenever the patients complained of pain and requested analgesic despite the above mentioned PCA therapy, meperidine 0.5 mg kg⁻¹ was intravenously administered as the rescue analgesia.

Further, 4 mg ondansetron (Zofer 4 mg/2 mL amp, Adeka İlaç and Kimyasal Ürünler San. and Tic. A.Ş. Istanbul, Turkey) was also intravenously prescribed every four hours on rescue antiemetic for all patients.

Table 1. Demographic data of groups (mean±SD)

	Group DT	Group LR	Group DS	Group S
Age (year)	55.2±12.6	54.6±17.1	51.9±11.7	48.5±12.7
Weight (kg)	73.6±9.0	73.8±13.7	65.5±11.6	67.8±15.5
Sex (male/female)	10/10	12/8	12/8	13/7
p>0.05. SD: standard deviation; DT: dexketoprofen; LR: lornoxicam; DS: diclophenac sodium; S: saline				

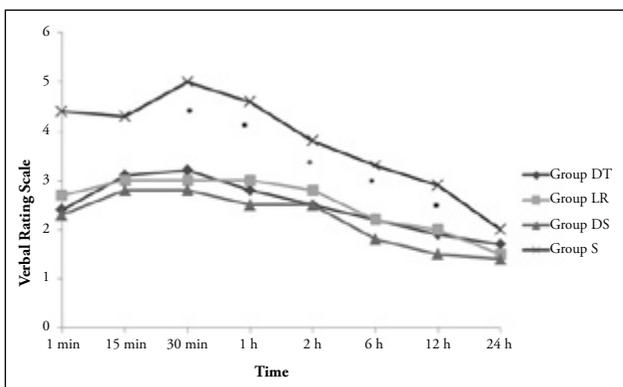


Figure 1. Pain scores in groups

*p<0.05 compared with group DT, LR, and DS

VRS: visual rating scale; DT: dexketoprofen; LR: lornoxicam; DS: diclophenac sodium; S: saline

Haemodynamic variables (HR, SBP, DBP), postoperative pain, sedation and patient comfort, cumulative tramadol consumption, supplemental rescue meperidine requirement and side effects were recorded by an anaesthetist of the Pain Management Team, who was blinded to the patient group, at the first, 15 and 30 min and at 1, 2, 6, 12 and 24 h after the start of PCA.

Postoperative pain was assessed by verbal rating scale (VRS) from 0 to 10 (0=no pain-10=imagined or the worst possible pain). Patient discomfort was assessed using an 11-point numerical scale from 0 to 10 (0=no discomfort-10=extreme discomfort). Sedation was assessed using a 5-point sedation scale with 1=awake and 5=deep sleep, no arousal.

Demographic data (age, weight, gender) and any side effects (nausea, vomiting, dermatitis, pruritus, dry mouth and urinary incontinence, NSAID-related cardiac and gastrointestinal side effects) associated with the study drugs were also recorded.

Statistical analysis

A power analysis was used to calculate the sample size. A 30% reduction in tramadol consumption has been reported as a clinically significant result (6). For a power of 0.9 using a significance level of 0.05, the required sample size was calculated as 20 subjects per study group or a total of 80 patients. The primary endpoint was defined as a 24-h tramadol consumption via patient-controlled analgesia.

Table 2. Postoperative patient comfort scores (mean±SD)

Time	Group DT	Group LR	Group DS	Group S	p value
1 st min	2.7±1.8	2.7±1.9	2.7±1.9	4.5±2.7	0.290
15 th min	2.9±1.4	3.2±1.6	3.0±1.8	4.1±2.2	0.961
30 th min	3.1±1.2	3.1±1.3	3.0±1.6	4.5±1.4	0.966
1 st h	2.3±0.8*	2.8±1.3*	2.8±1.6*	4.3±1.6	0.180
2 nd h	2.6±1.3*	2.7±1.2*	2.1±1.6*	4.1±1.9	0.011
6 th h	2.4±1.6*	2.5±1.1*	1.9±1.6*	3.5±2.3	0.013
12 th h	2.3±1.4*	2.1±1.1*	1.8±1.6*	3.1±2.2	0.001
24 th h	2.4±1.9*	1.8±1.2*	1.4±1.1*	2.9±2.3	0.001
0: no discomfort. 10: extreme discomfort, *p<0.01 compared with group S (Mann-Whitney U test), min: minute; h: hour; SD: standard deviation; DT: dexketoprofen; LR: lornoxicam; DS: diclophenac sodium; S: saline					

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 18.0 package program was used for statistical analysis. Categorical measurements are reported as the number and percentage and continuous measurements as the mean and standard deviation (if necessary median and minimum-maximum). The chi-square test was used to compare categorical measurements between the two groups. Repeated measures analysis was used to evaluate the results of the measurements between the groups in postoperative follow-up. In comparison of the measurements among the groups at different time points, if assumptions are provided, the one-way analysis of variance test, or if not, Kruskal-Wallis test was used. The Mann-Whitney U test was used with post hoc test (Bonferroni correction) in subgroup comparisons if there was a statistically significant difference. The level of statistical significance was considered as 0.05 in all tests.

Results

Eighty patients were included into the study, and all patients completed the study. The demographic data (age, weight, and sex) are shown in Table 1. No statistically significant difference was found between the groups in terms of demographic data and haemodynamic variables.

VRS scores were significantly decreased in group DT and LR compared with group S from the 30th min to the 24th h (p<0.001). It was significantly lower in group DS throughout the study period than in group S. However, there was no statistically significant difference in VRS scores between the treatment groups (Figure 1).

In comparisons of the groups, patient discomfort scores were found to be significantly higher in group S at 1, 2, 6, 12 and 24 h than in the other groups (p<0.01). It was significantly lower in group DS at 2, 6, 12 and 24 h after the start of PCA than in group DT and LR (p<0.01) (Table 2). There was no statistically significant difference in sedation scores between the groups (p>0.05).

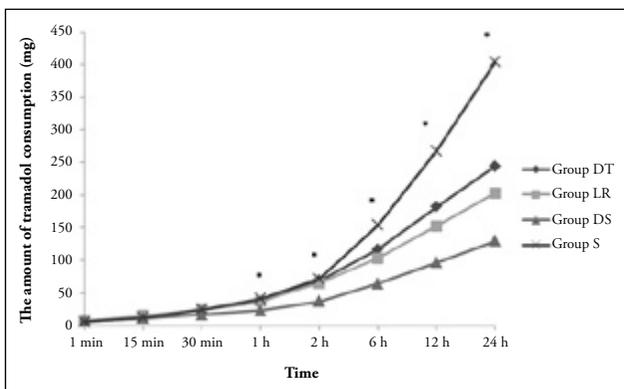


Figure 2. Postoperative amount of tramadol consumption (mg)
*p<0.05 compared with group DT, LR, and DS
DT: dexketoprofen; LR: lornoxicam; DS: diclophenac sodium; S: saline

Table 3. Supplemental analgesic (meperidine) requirement [n (%)]

Time	Group DT	Group LR	Group DS	Group S	p value
1 st min	0 (0%)	1 (5%)	0 (0%)	1 (5%)	0.572
15 th min	2 (2%)	0 (0%)	1 (5%)	3 (15%)	0.304
30 th min	1 (5%)	1 (5%)	1 (5%)*	6 (30%)	0.027
1 st h	0 (0%)*	2 (10%)*	1 (5%)*	6 (30%)	0.000
2 nd h	0 (0%)*	0 (0%)*	0 (0%)*	5 (25%)	0.000
6 th h	1 (5%)*	0 (0%)*	0 (0%)*	4 (20%)	0.017
12 th h	0 (0%)*	0 (0%)*	0 (0%)*	4 (20%)	0.006
24 th h	0 (0%)*	0 (0%)*	0 (0%)*	1 (5%)	0.394

*p<0.01 compared with group S (Mann-Whitney U test), min: minute, h: hour; SD: standard deviation; DT: dexketoprofen; LR: lornoxicam; DS: diclophenac sodium; S: saline

Table 4. Side effects [n (%)]

	Group DT	Group LR	Group DS	Group S
Nausea	8 (40%)	7 (35%)	5 (25%)	18 (90%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	1 (5%)
Dry mouth	3 (15%)	1 (5%)	1 (5%)	0 (0%)
Headache	3 (15%)	1 (5%)	0 (5%)	2 (10%)
Dermatitis	1 (5%)	0 (0%)	0 (0%)	1 (5%)

p>0.05. DT: dexketoprofen; LR: lornoxicam; DS: diclophenac sodium; S: saline

Cumulative tramadol consumption was significantly lower in group DS at each study period after the first postoperative hour than in group S (p<0.009). It was also significantly higher in group S at each study period after the second postoperative hour than in the other treatment groups (p<0.001). Furthermore, there was no significant difference in cumulative tramadol consumption between group DT and LR (Figure 2). The average supplemental rescue meperidine requirements were 25, 25, 37, and 57.7 mg in DT, LR DS, and S groups, respectively (Table 3). Supplemental meperidine

requirement was found to be significantly higher in group S at each study period after postoperative 30 min than in the other groups (p<0.01).

Thirty-eight patients (47%), i.e., 8 patients (40%) in group DT, 7 patients (35%) in group LR, 5 patients (25%) in group DS, and 18 patients (90%) in group S, experienced nausea despite antiemetic prophylaxis and were treated with 4 mg IV ondansetron. The incidence of nausea was significantly higher in group S than in the other groups. One patient in the S group experienced vomiting two hours after PCA therapy. NSAID-related cardiac or gastrointestinal side effects were not observed (Table 4).

Discussion

Multimodal analgesic techniques, involving the use of smaller doses of opioids with NSAIDs, are becoming increasingly popular approaches after major surgical procedures (7, 8). In the present study, to augment analgesic potency and reduce tramadol consumption, three different IV NSAIDs were used in combination with tramadol PCA.

A synergistic association between opioids and NSAIDs has been studied in many experimental and clinical trials (9, 10); however, trials evaluating the synergism are inconsistent (11, 12). Better antinociceptive activity with dexketoprofen+tramadol was not confirmed in an experimental study using the formalin assay for orofacial pain (12). Our study, with its reductions in pain scores and cumulative tramadol consumption after 24 h, supports the synergism between tramadol and NSAIDs in the treatment groups.

Clinical studies with dexketoprofen have demonstrated a synergistic association between analgesics and dexketoprofen when used at the doses between 12.5 and 100 mg (13, 14). In a prospective, randomized, controlled study, Iohom et al. (14) investigated the effect of dexketoprofen on opioid requirements and inflammatory response following elective hip arthroplasty. They stated that the perioperative administration of 25 mg dexketoprofen markedly improves postoperative analgesia and decreases morphine requirements following hip arthroplasty. In our study, similarly, we found better analgesia, lower tramadol consumption, and less supplemental rescue analgesic requirement in all treatment groups.

Lornoxicam has also been shown to reduce postoperative opioid consumption when combined with opioids (15, 16). However, studies regarding the analgesic efficacy of lornoxicam have shown conflicting results. Korkmaz Dilmen et al. (17) stated that 8 mg lornoxicam is not enough to address the effective pain control after lumbar disc surgery. However, Isik et al. (18) compared analgesic efficacy of preoperative 8 mg lornoxicam with IV 50 mg tramadol for postoperative pain relief after tonsillectomy in adult patients. In that study, they found that 8 mg lornoxicam was associated with better analgesic potency and similar side effects compared with

50 mg tramadol. Olmez et al. (19) compared the analgesic efficacy of lornoxicam with tramadol during transrectal ultrasound-guided biopsy of the prostate. In that controlled study, they reported a better pain and patient comfort scores with tramadol than with lornoxicam. Kemal et al. (20) compared analgesic efficacy of tramadol alone and with the combinations of metamizol+tramadol and lornoxicam+tramadol by PCA for postoperative pain management after lower abdominal surgery. In that study, combination therapies resulted in better postoperative pain management, lower tramadol consumption and lesser side effects compared with tramadol group. These results were similar to our findings, wherein a combination of lornoxicam with tramadol PCA markedly reduced tramadol consumption. The number of patients requiring supplemental meperidine was also significantly higher in the placebo group at 30 min, and at 1, 2, 6, and 12 h than in the treatment groups.

In a systematic review, paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side effects have been compared after a major surgery (7). In that study, they found that treatment groups markedly reduced the amount of morphine consumption (6.34 mg, 10.18 mg, and 10.92 mg in paracetamol and selective and non-selective non-steroidal anti-inflammatory groups, respectively). They also stated that the incidence of postoperative nausea and vomiting was significantly lower with NSAIDs than with placebo (odds ratio 0.70; 95%). Last, they concluded that when paracetamol, NSAID, or COX-2 inhibitors are administered in addition to PCA morphine after surgery markedly lowered morphine consumption at 24 h compared with PCA morphine+placebo. However, no benefit was noted in terms of reduction in morphine-related adverse effects when three non-opioid analgesics were combined with PCA morphine (7).

Sivrikoz et al. (21) have recently compared the efficacy of 50 mg dexketoprofen and 8 mg lornoxicam on morphine consumption after a major orthopaedic surgery and have found that dexketoprofen has a superiority over lornoxicam in analgesic efficacy and morphine consumption.

A placebo-controlled study comparing the analgesic efficacy of ketoprofen and diclophenac and their effects on opioid (oxycodone) consumption after total knee arthroplasty has revealed considerable analgesic efficacy and opioid sparing effects with dexketoprofen on the first day (between 13 and 24 h), whereas at the second postoperative day (between 25 and 60 h), these effects were more pronounced with diclophenac sodium than with placebo (22).

However, contrary results have also been reported. In a clinical study comparing the analgesic efficacy of lornoxicam and diclophenac, similar analgesic efficacy for postoperative pain after coronary artery bypass graft surgery has been determined (23). Sener et al. (24) compared the analgesic efficacy of IV lornoxicam for the management of postoperative

pain with diclophenac, ketoprofen, dipiron, and placebo and have reported that 16 mg day⁻¹ lornoxicam, 150 mg day⁻¹ diclophenac, 200 mg day⁻¹ ketoprofen, and 3 g day⁻¹ dipyrone provides a similar analgesic effect. The analgesic efficacy of lornoxicam was similar but not superior to that of the other analgesics administered (24). In our study, VRS scores markedly decreased in group dexketoprofen and lornoxicam compared to group saline from the 30th min to the 24th h. However, no statistically significant difference was noted in VRS scores between the treatment groups.

In many studies, diclophenac has been shown to have potent inhibitory effect on prostaglandin synthesis (22, 25). The better analgesic action of diclophenac after 24 h, when compared to lornoxicam and ketoprofen, supports the assumption that diclophenac may also act by different mechanisms other than peripheral inhibition of prostaglandin synthesis. In an *in vivo* experimental study, diclophenac sodium has been reported to have a stronger anti-inflammatory effect than ketoprofen (25). Furthermore, a metabolite of diclophenac has also shown to have a marked anti-inflammatory action, much greater than that exerted by other NSAIDs (26, 27). Our lower pain scores and fewer tramadol consumptions in patients receiving diclophenac may be attributable to a stronger anti-inflammatory effect of diclophenac than that of other NSAIDs.

It is well known that tramadol is associated with postoperative nausea and vomiting (PONV) (28). In our study, the incidence of PONV was lower with the coadministration of dexketoprofen, diclophenac, or lornoxicam with tramadol than that of control group. Our lower nausea rates in patients who received combined therapy may be attributable to lower pain scores, less tramadol, and rescue meperidine consumption.

Zippel et al. (3) report that intravenous dexketoprofen is associated with serious cardiac or gastrointestinal side effects, including myocardial ischemia and haemorrhagic events. In our study, haematological or cardiac side effects were not associated with NSAIDs throughout the study period.

A limitation of this study was not determining the optimum dosage of each analgesic. Limited studies are present to guide the possible combinations. We combined three different NSAIDs with tramadol; however many combinations and dosages of treatment agents were also possible to provide optimal analgesia. We were unable to achieve optimal dosages of the study drugs. Further studies and combinations are required to reveal this association.

Conclusion

After a major abdominal surgery, adding IV diclophenac, lornoxicam, or dexketoprofen to patient-controlled tramadol resulted in lower pain scores, smaller tramadol consumption, lesser rescue supplemental analgesic require-

ment, and fewer side effects than tramadol alone group. Tramadol consumption was the lowest in the diclophenac sodium group compared to lornoxicam and dexketoprofen after 24 h.

Ethics Committee Approval: Ethics Committee Approval was received for this study from Turkey: Health of Ministry Clinical Drug Research Ethics Committee-II (2010-31).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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