The efficacy of adding dexketoprofen trometamol to tramadol with patient controlled analgesia technique in post-laparoscopic cholecystectomy pain treatment

Laparoskopik kolesistektomi sonrası ağrı tedavisinde hasta kontrollü analjezi yönteminde tramadole deksketoprofen trometamol eklenmesinin etkinliği

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Summary

Objectives: Pain treatment in laparoscopic cholecystectomy, which is performed in increasing numbers as an ambulatory procedure, is an important issue.Although laparoscopic cholecystectomy is regarded as an ambulatory procedure, patients are often hospitalized due to pain and this increases opioid consumption and side effects caused by opioids. This study aims at evaluating the efficacy of adding dexketoprofen trometamol to tramadol with patient controlled analgesia (PCA) in post-laparoscopic cholecystectomy pain treatment.

Methods: 40 patients in ASA I-II risk groups aged between 18-65 years were enrolled in the study and were randomized using closed envelope method. In Group TD 600 mg tramadol and 100 mg dexketoprofen trometamol, in Group T 600 mg tramadol was added to 100 ml 0.9% normal saline for PCA. 8 mg lornoxicam iv was given if VAS >40 in the postoperative period.

Results: There was no statistically significant difference in terms of adverse effects (hypotension, bradycardia, sedation) but in Group T 4 patients complained of nausea and 3 complained of vomiting. Opioid consumption was lower and patient satisfaction was higher in group TD.

Conclusion: This study has shown that adding dexketoprofen trometamol to tramadol in patient controlled analgesia following laparoscopic cholecystectomy lowers VAS scores, increases patient satisfaction and decreases opioid consumption.

Key Words: Dexketoprofen trometamol; laparoscopic cholecystectomy; patient controlled analgesia; postoperative pain.

Özet

Amaç: *Giderek artan sayıda yapılan günübirlik bir cerrahi girişim olan laparoskopik kolesistektomide ağrı tedavisi önemli bir sorundur. Her ne kadar laparoskopik cerrahi günübirlik bir girişim olarak kabul edilse de, hastalar sıklıkla ağrı nedeniyle hospitalize edilmekte ve bu da opioid tüketimini ve opioidlerin sebep olduğu yan etkileri arttırmaktadır. Bu çalışmanın amacı, laparoskopik kolesistektomi sonrasında ağrı tedavisi için hasta kontrollü analjezi (PCA) yönteminde tramadole deksketoprofen trometamol eklenmesinin etkinliğini araştırmaktır.*

Gereç ve Yöntem: *Çalışmaya 18-65 yaşları arasında ASA I-II risk grubundan 40 hasta alındı ve kapalı zarf yöntemi ile randomize edildi. Grup TD'de 600 mg tramadol ve 100 mg deksketoprofen, Grup T'de ise 600 mg tramadol 100 ml %0.9 normal saline eklenerek PCA hazırlandı. Postoperatif dönemde VAS >40 olması durumunda 8 mg lornoksikam iv verildi.*

Bulgular: *Yan etki profili açısından (hipotansiyon, bradikardi, sedasyon) iki grup arasında istatistiksel olarak anlamlı bir fark yoktu, fakat Grup T'de 4 hasta bulantıdan, 3 hasta ise kusmadan yakındı. Grup TD'de opioid tüketimi daha düşük ve hasta memnuniyeti daha yüksekti.*

Sonuç: *Bu çalışma laparoskopik kolesistektomi sonrasında tramadole deksketoprofen trometamol eklenmesinin hasta kontrollü analjezi yönteminde VAS skorlarını düşürdüğünü, hasta memnuniyetini arttırdığını ve opioid tüketimini azalttığını göstermiştir.*

Anahtar sözcükler: Deksketoprofen trometamol; laparoskopik kolesistektomi; hasta kontrollü analjezi; postoperatif ağrı.

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Introduction

Pain treatment in laparoscopic cholecystectomy, which is performed in increasing numbers as an ambulatory procedure, is an important issue.[1] Nonsteroid antiinflammatory drugs (NSAIDs) are often utilized in postoperative analgesia because they have analgesic effects comparable to opioids but lack the adverse effects of opioids. NSAIDs are a wide group of agents which have analgesic, antipyretic and antiinflammatory properties. The mechanism of action of these drugs is the inhibition of cyclo-oxygenase (COX) enzyme family which is responsible of prostaglandin synthesis.[2] Dexketoprofen is the S(+) enantiomer of ketoprofen, which is a COX-1 and COX-2 inhibitor arylpropyonic acid.[3] Recently there is a trend to synthetise the enantiomers of various drugs which give these agents a more controlled profile and minimize their adverse effects.[3,4] Studies conducted on patients with acute and chronic pain have shown that oral dexketoprofen has a high analgesic activity and tolerability.[5,6] Previous studies have compared equivalent doses of racemic ketoprofen and dexketoprofen.[6,7] Although laparoscopic cholecystectomy is regarded as an ambulatory procedure, patients are often hospitalized due to pain[8] and this increases opioid consumption and side effects caused by opioids. Combination of NSAIDs with opioids decrease the incidence of respiratory depression and over sedation while increasing cooperation and mobility and recovery of intestinal function faster.[9] Although intravenous dexketoprofen trometamol has been used in acute postoperative pain treatment[10,11] there are not enough studies on opioid and dexketoprofen trometamol combination in patient controlled analgesia technique.

The primary endpoint of this study was to investigate the effect of adding intravenous dexketoprofen trometamol to tramadol on postoperative VAS scores in postoperative laparoscopic cholecystectomy pain. The secondary endpoint was to investigate the effect of this combination on the postoperative patient satisfaction, opioid consumption and side effects related to opioids.

Materials and Methods

After obtaining the approval of Ufuk University ethical committee, 40 patients in ASA I-II risk groups aged between 18-65 years were enrolled in the study and were randomized using closed envelope method. Written consent forms were obtained from all patients. Exclusion criteria were morbid obesity, NSAID allergy, existence of serious hepatic, renal and gastric disease, usage of sedatives or anxiolytics in the previous month, alcohol abuse and usage of NSAIDs or any analgesics 12 hours prior to the study (24 hours for long-acting NSAIDs). Upon arrival to the operating room, heart rate, systolic, diastolic and mean arterial pressures were measured and ECG and pulse oxymeter monitorization were performed. All patients were premedicated using midazolam (Dormicum®, 5 mg / 5 ml, F. Hofmann-La Roche, Fontenay, France) (iv) 0.03 mg/kg 10 minutes prior to induction. 50 mg dexketoprofen trometamol and 50 mg tramadol were given intravenously before the induction. Propofol (Propofol-® Lipuro 1%, 10 mg/ml B. Braun, Melsungen, Germany) 3 mg/kg, rocuronium (Esmeron® 50 mg/ 5 ml, Schering-Plough, Organon Oss, Holland) 0.6 mg/kg and 50 mg ranitidine (Ulcuran® 50 mg/ 2 ml, Mefar Pharmaceuticals, Istanbul, Turkey) were used for induction. For maintenance sevoflurane (Sevorane®, Abbott Laboratories, England) 2-3% and 50% O_2-air mixture was used. Heart rates and

Table 1. Demographical data

	Group TD (n=20)	Group T (n=20)	p
Age (years)	48.3±15.2	51.7±13.4	0.458
Height (cm)	78.8±13.9	77.8±12.6	0.803
Weight (kg)	167.5±7.4	168.7±10.3	0.675
Gender (F/M)	13/7 (65%; 35%)	11/9 (55%; 45%)	0.747
Surgery time (min)	67.8±30.9	61.5±41.5	0.590
Time to extubation (min)	5.0±3.4	3.6±2.3	0.201

Table 2. Demand values (Average±Standard Deviation [Median])

	Group		p
	TD	T	
Po 2nd hour	2.7±2.9 (2)	4.7±3.1 (3)	0.023
Po 4th hour	4.1±3.4 (4)	6.2±3.2 (5)	0.020
Po 6th hour	5.1±3.7 (5)	8.0±3.5 (7)	0.017
Po 12th hour	6.7±4.0 (7)	9.8±3.8 (9)	0.023
Po 24th hour	8.6±5.5 (8.5)	11.9±4.3 (11)	0.038

Values are the number of bolus demands made by the patient.

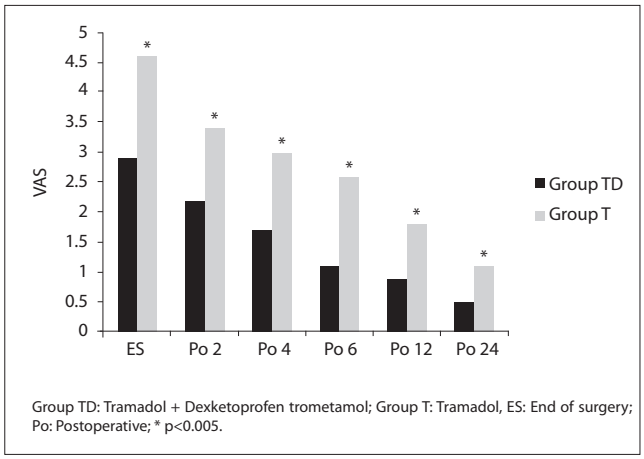
mean arterial pressures were recorded before intubation and 1, 5, 10, 20, 30, 45, 60 and 90 minutes after intubation. Heart rate and mean arterial pressures were recorded at the end of surgery and 20, 40, 60 minutes after the end of surgery, visual analogue score (VAS), adverse effects caused by study drugs (nausea, vomiting, pruritus, hypotension, hypertension, bradycardia, tachycardia and sedation) in the 2, 4, 6, 12 and 24 hours after start of patient controlled analgesia (PCA) and demand, delivery and total consumption values were recorded. Patient satisfaction was measured using Likert scale[12] at the end of the 24th hour (1: Completely comfortable, 2: Very comfortable, 3: Slight discomfort, 4: Painful 5: Very painful). Sedation was measured using the Ramsey sedation scale (1: Anxious, restless or both, 6: No response to stimulus). In Group TD 600 mg tramadol (Contramal® 100 mg / 2 ml, Abdi İbrahim, Istanbul, Turkey) and 100 mg dexketoprofen trometamol (Arveles®, A. Menarini International, Florence, Italy), in Group T 600 mg tramadol was added to 100 ml 0.9% normal saline for PCA. In both groups PCA was set to 3 ml bolus, 15 minutes lock out time and 15 ml 4 hours limit. 8 mg lornoxicam (Xefo®, 8 mg, Nycomed, Denmark) iv was given if VAS >40 in the postoperative period. 50 mg ranitidin iv was given if the patient complained of gastrointestinal discomfort and 8 mg ondansetron iv was given if the patient complained of nausea. PCA was stopped at the 24th hour of the study.

For statistical analysis SPSS for Windows version 15.0 was used. Numerical variables were shown using average, standard deviation, median and qualitative variables were shown using numbers and percentage. Difference in numerical variables among groups was evaluated using t test or Mann-Whitney test depending on distribution of variables, chi-square test was used to evaluate the difference in qualitative differences. Changes in heart rate and mean arterial pressure values were evaluated using variance analysis. Mann-Whitney test was used to evaluate the difference between groups in VAS, demand and delivery values and intergroup changes were evaluated using Friedman test. Statistical significance was set as p=0.05.

VAS values were used to calculate the sample size. The number of patients necessary to find a difference of 1.8 units was determined to be 20. When calculating the sample size, level of uncertainty (α) was set as 0.05 and power (1-ß) was set as 0.80.

Results

A total of 44 patients were enrolled to the study but 3 were excluded because of switching to laparotomy



Group TD: Tramadol + Dexketoprofen trometamol; Group T: Tramadol, ES: End of surgery; Po: Postoperative; * p<0.005.

Fig. 1. VAS scores.

Table 3. Delivery values (Average±Standard Deviation [Median])

	Group		p
	TD	T	
Po 2nd hour	1.7±1.5 (2)	2.5±0.9 (2)	0.035
Po 4th hour	2.7±1.7 (2.5)	4.4±2.1 (4)	0.018
Po 6th hour	3.5±2.1 (4)	5.6±2.6 (4.5)	0.026
Po 12th hour	4.6±2.4 (4.5)	6.6±2.9 (6)	0.028
Po 24th hour	5.8±3.5 (6)	8.1±3.2 (8)	0.026
Total opioid consumption (mg)	104.4±63	145±57.6	0.040
Additional analgesics	7/13 (35%; 65%)	9/11 (45%; 55%)	0.747

Values are the number of boluses delivered to the patient.

and 1 was excluded due to difficulty in cooperation and the study was completed with 40 patients. There was no statistically significant difference in demographical data between patient groups (Table 1).

There was no difference between vital signs in the intraoperative period (heart rate, mean arterial pressure). VAS was higher in Group T ($p<0.005$) (Figure 1). VAS values were higher in Group T compared to Group TD at all intervals. Demand and delivery in Group TD was lower than in Group T on 2, 4, 6, 12 and 24th hours (Table 2 and Table 3). Four patients were "painful" and two patients in Group T were "very painful". 9 patients in Group T and 7 patients in Group TD needed additional analgesics.

There was no statistically significant difference in terms of adverse effects (hypotension, bradycardia, sedation) but in Group T 4 patients complained of nausea and 3 complained of vomiting. The total opioid consumption was calculated by multiplying the number of deliveries at the end of the 24th hour by the number of boluses (one bolus is 3 ml and 18 mg tramadol). The total opioid consumption in Group T was 145 mg, in Group TD was 104.4 mg ($p=0.040$, average values, Table 3). Overall patient satisfaction was significantly higher in Group TD (Table 4). There was no difference between groups in terms of additional analgesic requirement.

Table 4. Patient satisfaction (Likert scale)

	Group		p
Patient satisfaction, n (%)	**TD**	**T**	
Completely comfortable	14	9	
Quite comfortable	5	2	
Slight discomfort	1	3	0.019
Painful	0	4	
Very painful	0	2	

Discussion

NSAIDs are a group of drugs which find a wider area of utilization in the multimodal treatment of postoperative pain. In a study which evaluated 60 abdominal hysterectomy patients, oral rofecoxib 50 mg lowered postoperative tramadol PCA consumption and VAS scores.[13] The results of this study which evaluates adding dexketoprofen trometamol to tramadol show that total opioid consumption, VAS values were significantly lower while patient satisfaction was higher in the dexketoprofen trometamol group.

Laparoscopic cholecystectomy causes moderate to severe pain in the postoperative period. The intensity of pain after the procedure depends on the residual gas volume, pressure caused by the pneumoperitoneum and the speed of insufflation.[14] In order to eliminate all these variables the procedure was performed by the same surgical team in similar durations.

NSAIDs have been used for postoperative analgesia in laparoscopic cholecystectomy as a sole agent, Wilson et al. have shown that diclofenac effectively lowers postlaparoscopic cholecystectomy pain, similarly Liu et al reported that preoperative 30 mg intravenous ketorolac decreased analgesic requirements af-

ter laparoscopic cholecystectomy.[15,16] However, it has been shown that their combination with opioids provide more effective pain control[17] and reduces opioid consumption and associated side effects as the results of a study by Iohom et al., which was conducted on 30 total hip arthroplasty patients and 25 mg dexketoprofen was used transdermally 24 hours before and 48 hours after the surgery suggests.[18] Similarly, in this study, addition of dexketoprofen trometamol to tramadol has significantly decreased VAS scores in the postoperative period which is the primary endpoint. As a result, opioid consumption was lower and patient satisfaction was higher in the dexketoprofen trometamol group which was the secondary endpoint of this study. The incidence of side effects was lower in group TD, although it is not statistically significant, this may be clinically relevant, which was also a secondary endpoint.

Currently there is a trend to investigate the pure enantiomeric forms of racemic drugs in order to obtain the desired effect in lower doses and to reduce the incidence of side effects. Ketoprofen, (+-)-(R,S)-2-(3- benzoilphenyl) propionic acid, is a chiral 2-arylpropionic acid derivative with nonsteroid antiinflammatory effects. Dexketoprofen trometamol, which is a water soluble S(+)-enantiomere of ketoprofen, has a faster onset, lower gastrointestinal side effect profile and higher potency compared to the racemic compund.[3] On the other hand, R(-) ketoprofen has a lower COX inhibition effect and a prostaglandin independent ulcer formation effect.[19]

There are numerous studies in literature where oral and intravenous dexketoprofen trometamol has been used in postoperative pain treatment. Iohom et al. have investigated the effect of preemptive oral dexketoprofen trometamol and placebo on opioid consumption and shown that dexketoprofen trometamol lowers both opioid consumption and side effects caused by opioids significantly.[18] Hanna et al. have investigated the effect of intramuscular dexketoprofen, ketoprofen and placebo on postoperative pain treatment after major orthopedic surgery and shown that 50 mg intramuscular dexketoprofen provides adequate analgesia and lowers morphine consumption.[20] In a multi-center study in which 25 and 50 mg intravenous dexketoprofen bolus and 2 g intravenous dipyrone is compared in acute renal colic patients, Sanchez-Carpena et al. have shown that dexketoprofen is equally effective and safe as dipyrone and additionally has a faster onset of action.[11]

In a study conducted on 210 patients for dental surgery, dexketoprofen 12.5 mg, 25 mg and 50 mg has been compared with ketoprofen 50 mg in dental pain and has been shown to have a similar analgesic efficacy but a faster onset of action.[6] Similar results have been obtained in patients with primary dysmenorrhea where oral dexketoprofen 12.5 and 25 mg was compared with ketoprofen 50 mg.[7] A new form of dexketoprofen suitable for parenteral usage has been developed recently and has ben shown to be effective in various pain scenarios such as renal colic where dexketoprofen 25 mg and 50 mg intramuscular was compared with dipyrone 2 g intramuscular for the treatment of renal colic by Sanchez-Carpena et al.[21] However, there is not sufficient data on usage of dexketoprofen trometamol for postoperative pain control using patient controlled analgesia method.

In this context, dexketoprofen trometamol appears to be promising in pain treatment after laparoscopic cholecystectomy.

Joris et al. have defined the pain experience after laparoscopic cholecystectomy as visceral, abdominal wall and pain referring to shoulder and have stated that in the postoperative first day, visceral pain is more discomfortable than abdominal wall pain. In the mentioned study, they compared intraperitoneal bupivacaine with saline and found that intraperitoneal bupivacaine is not effective for treating postlaparoscopic cholecystectomy pain.[22] The pain control method utilized in this study aims to control the incisional pain rather than visceral pain. In a study conducted by Ure et al., the most intensive pain was in the right upper quadrant and port entry sites in the first 24 hours following the procedure.[23] The pain type in this study is in accordance with the observations made by Ure et al. Additionally, the preemptive efficacy of NSAIDs[16] and tramadol[24] is well known and have been used in this study.
The fact that four patients were “painful” and two patients were “very painful” in Group T has been linked to the length of surgery and extent of tissue

trauma caused by surgery. These patients were given tramadol boluses and additional analgesics.

Nausea was observed in 4 patients and vomiting was observed in 3 patients in Group T. The fact that nausea and vomiting were observed only in Group T can be caused by the higher opioid consumption. The sample size of this study was calculated to evaluate the difference in VAS scores, for evaluating nausea/vomiting a bigger sample size can be necessary.

In conclusion, dexketoprofen trometamol added to opioids for postoperative analgesia after laparoscopic cholecystectomy lowers VAS scores, decreases opioid and additional analgesic requirements and increases patient satisfaction. Using dexketoprofen trometamol as a sole agent in patient controlled analgesia rather than a combination with opioids may help avoid the adverse effects of opioids. Further studies may focus on using dexketoprofen trometamol in different settings such as thoracotomy or major abdominal surgery.

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