The Effect of Preemptive Intravenous Dexketoprofen Trometamol on Quality of Patient-Controlled Analgesia After Abdominal Hysterectomy

Preemptif İntravenöz Dexketoprofen Trometamol'ün Abdominal Histerektomi Sonrası Uygulanan Hasta Kontrollü Analjezi Kalitesine Etkisi

Preemptif Intravenöz Dexketoprofen Trometamol / Preemptif intravenöz Dexketoprofen Trometamol

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Özet

Amaç: Abdominal histerektomi öncesi preemptif i.v Deksketoprofen Trometamol (DKP)' ün patient controlled analgesia (PCA) 'de kullanılan fentanil dozu, yan etkiler ve hasta memnuniyetine olan etkisini incelemeyi amaçladık. Gereç ve Yöntem: Etik onay dan sonra ASA I-II abdominal histerektomi uygulanacak 40 hasta randomize olarak iki gruba ayrıldı. Her iki gruba standart anestezi uygulandı. Grup F (n=20): Operasyon dan 30 dakika önce ve ilk dozdan 8 saat sonra plesebo; Grup D (n=20): Operasyon dan 30 dakika önce ve ilk dozdan 8 saat sonra i.v 50mg Deksketoprofen trometamol verildi. Her iki gruba derlenme odasında VAS>3 olduğunda, 1.5µg/kg fentanil uygulandı. Yeterli analjezi sağlanamazsa (VAS≤3) 10 dk ara ile 25µg ilave edildi ve sonrasında analjezi, PCA ile (bolus doz 25 µgr fentanil, kilitli kalma süresi 10 dakika; 4 saatlik limit 400 µg) sağlandı.VAS scoru, sedasyon scoru, fentanil tüketimi, PONV ve yan etkiler kaydedildi. Bulgular: Demografik veriler benzerdi. Her iki grupta da solunum depresyonu görülmedi. VAS skoru açısından anlamlı farklılık yoktu (p=0.07). Postoperatif bulantı kusma fentanil grubunda DKP eklenen gruba göre anlamlı yüksekti (p=0.03). PONV skoru postoperatif 12. ve 24. Saatte Grup D de Grup F den önemli oranda düşüktü (p=0.03). Fentanil tüketimi postoperatif 12. ve 24. Saatte Grup D de Grup F den önemli oranda düşüktü (P=0.001). Sonuç: 50 mg intravenöz DKP verilen olgularda Fentanil tüketiminin 40 % azalmasına bağlı olarak analjezi kalitesinin artıp, yan etki insidansını azalttığını gözlemledik.

Anahtar Kelimeler

Dexketoprofen; Trometamol; Abdominal Histerektomi; Fentanil

Abstract

Aim: We investigated the fentanyl dose used in patient-controlled analgesia (PCA) of preemptive intravenous (IV) dexketoprofen trometamol (DKP) after abdominal hysterectomy. Material and Method: Following approval by the local ethics committee, 40 patients scheduled for ASA I-II abdominal hysterectomy were randomly divided into two groups. The anesthetic techniques were standardized. Group F (n=20): Placebo administered 30 minutes prior to operation and after 8 hours; Group D (n=20): 50mg IV dexketoprofen trometamol administered 30 minutes prior to operation and after 8 hours. When VAS>3, 1.5 µg/kg fentanyl was administered to both groups in the recovery room. At intervals and afterwards, analgesia was provided through PCA (bolus dose: 25 µg fentanyl; lock out period: 10 min.; 4-hr limit: 400 µg). VAS score, sedation score, fentanyl consumption, postoperative nausea and vomiting (PONV), and side-effects were recorded. Results: Demographic data and duration of surgery in the two groups were similar. Respiratory depression was not seen in either group. There was no significant difference based on the VAS score (p= 0.07). Nausea and vomiting were significantly higher in the Group F compared to Group D (p=0.03). Compared to Group F, PONV were less in Group D, at 12hr and 24hr postoperatively (p=0.03). Fentanyl consumption at 12 and 24 hours was lower in Group D than Group F (p=0.001). Discussion: In cases where 50 mg of intravenous dexketoprofen trometamol was administered, we observed that the fentanyl consumption decreased by 40%, analgesia quality increased and the incidence of side-effects decreased.

Keywords

Dexketoprofen; Trometamol; Abdominal Hystorectomy; Fentanyl

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Introduction

Preemptive analgesia should start prior to surgery and should continue while the nociceptors at the site of the wound are stimulated [1,2]. In the pathogenesis of post-operative pain, neuronal plasticity, central sensitization and increase in COX-2 play a role. Therefore, as a new pain control procedure, a multimodal analgesic method is adopted, in which analgesics are used in combination at the perioperative stage, in order to control the pain caused by nociceptive and central stimulation [3]. Multimodal analgesia refers to the use of two or more agents. With this method, the side-effects due to high doses are minimized, while maximally benefiting from the analgesic effect of each agent [4,5]. Fentanyl and its derivatives are frequently used in clinical settings. Although these are effective in pain treatment, fentanyl requires continuous administration, as it has a very short therapeutic effect due to its fast metabolization [6,7]. Dexketoprofen trometamol is a non-steroid, anti-inflammatory (NSAID) drug that has a racemic ketoprofen inactive enantiomer, and belongs to the arylpropionic acid group [8]. Recently, there has been a rapid increase in the use of latest generation NSAIDs. Compared to classic NSAIDs, these drugs, such as dexketoprofen trometamol, have fewer side-effects and higher efficacy [8]. Unwanted side-effects of fentanyl can be reduced by reducing the therapeutic analgesic dose, which can be accomplished by an enhancement with dexketoprofen trometamol.

In the present study, we examined the fentanyl dose used in patient-controlled analgesia (PCA) of intravenous (IV) dexketoprofen trometamol in abdominal hysterectomy, its side-effects, especially postoperative nausea and vomiting (PONV), quality of pain relief and patient satisfaction.

Material and Method

After obtaining approval from the Atatürk University ethics committee and informed consent, 40 patients who were scheduled to undergo ASA I-II abdominal hysterectomy were randomly divided into two groups. The study excluded patients who developed complications during the operation; were allergic to NSAID; had blood clotting problems or blood dyscrasia; were identified as having malignity or used cytotoxic drugs; complained of asthma and were sensitive to aspirin; had gastrointestinal disease (GID) (gastritis, ulcer, esophageal varices during the pervious 6-month period); had coronary artery disease; congestive heart failure; valvular heart disease; participated in any type of drug research study during the previous 30 days; were pregnant; had kidney failure, alcohol dependency or respiratory problems. The patients were informed about the application and about patient-controlled analgesia (PCA). All patients were monitored by electrocardiography (ECG), noninvasive blood pressure, and pulse oximetry when they arrived at the operating theater. The anesthetic techniques were standardized. Anesthesia was achieved using 1.5-2 mg/kg of propofol and 1 μg/kg of remifentanil. In order to achieve neuromuscular blockade, 0.8 mg/kg of IV rocuronium was administered. The lungs were ventilated using 50% air in oxygen, subsequent to tracheal intubation. Anesthesia was maintained with sevoflurane 1-2% and 66% N2O/O2. No other analgesic, antiemetic or sedative drug was used in order to maintain anesthesia. Group F (n=20) received: Placebo, administered 30 minutes prior to operation and after 8 hours; Group D (n=20) received: 50 mg of IV dexketoprofen trometamol (Arveles amp (2ml) I.E ULAGAY, Italy), administered 30 minutes prior to operation and after 8 hours. Prior to operation, Group D was given 50 mg of ranitidine (Ulcuran amp 50mg, ABFAR, Turkey). At the end of surgery, neuromuscular block was reversed with 0.03 mg/kg of neostigmine and 0.004 mg/kg of atropine, administered by IV. After adequate spontaneous respiration, the trachea was extubated. In the recovery room, 1.5 μg/kg fentanyl was administered to both groups, when VAS>3. Where sufficient analgesia was not achieved (VAS≤3), 25 μg was added at 10-minute intervals and any further analgesia was provided through PCA (bolus dose: 25 μg fentanyl; lock out period: 10 min.; 4-hr limit: 400 μg). During the operation, EKG, heart rate (HR), non-invasive systolic-diastolic blood pressure (SBP-DBP), mean arterial blood pressure (MAP) and peripheral oxygen saturation (SpO2) were monitored. If the blood pressure was 20% lower for longer than 60 seconds, it was defined as hypotension, and a heart rate (HR) of <50/min was defined as bradycardia. When hypotension was observed, the plan consisted of an initial fluid treatment followed by the administration of vasoconstrictor agent (ephedrine 5-10mg). In the case of bradycardia, an anticholinergic (atropine sulfate 0.015 mg/kg) was to be administered. The intensity of pain was measured using a 10-cm visual analogue scale (VAS). The extreme left was labeled 'no pain at all' and the extreme right indicated 'intolerable pain'. The patients were monitored at 2, 4, 12 and 24 hours post-operatively, using VAS score, sedation score, nausea-vomiting score, patient satisfaction scale, blood pressure and heart rate. Side-effects (pruritus, nausea, vomiting, sedation, respiratory depression) and total fentanyl use were recorded. Sedation score was measured on a four point scale: 1= awake, 2=drowsy, 3=asleep, easily arousable, 4= asleep, difficult to rouse. The severity of PONV [9,10] was further analyzed using a 4-degree categorization that utilizes a scoring algorithm that has also been used in other studies, where: 0 (No PONV) : Absence of any emetic episodes and nausea. 1 (Mild PONV): 1:1) Mild nausea present; 1:2) One emetic episode or short lasting nausea of any severity (< 10 min) occurred and no antiemetic drugs were necessary. 2 (Moderate PONV): 2:1) One or two emetic episodes or moderate to severe nausea without exogenous stimulus; 2:2) Patients required antiemetic therapy once. 3 (Severe PONV): More than 2 emetic episodes or nausea occurring more than twice (moderate or severe); the administration of at least more than 1 antiemetic was necessary. Patient satisfaction was measured based on a 4-point scale (1=completely dissatisfied, 2=slightly dissatisfied, 3=significantly satisfied, 4=completely satisfied).

In order to decrease the dose of dexketoprofen trometamol and fentanyl by 30%, the number of patients required for each group was determined to be at least 19, using power analysis, where 80% (1-β) and α=0.05; therefore, each group-size contained 20 people. Nausea, vomiting, pruritus and patient satisfaction were analyzed as secondary results. The Mann-Whitney U test was used, where $p<0.05$ was considered significant.

Results

Demographic data and the duration of surgery in the two groups

Table 1. Demographic data

	Group F (n=20)	Group D (n=20)
Age (yr)	55.1 ± 5.9	58.2 ± 5.6
Weight (kg)	73.8 ± 7.5	74.9 ± 10.5
Height (cm)	158 ± 6.2	161 ± 8.4
Surgical time (min)	120.4 ± 11.7	118.4 ± 7.3

Values are mean ± SD. No significant differences between the group (p>0.05).

Table 2. Sedation score

Sedation score	Gorup F (n=20)	Group D (n=20)
4.hour		
1	11(55%)	15 (75%)
2	9 (45%)	5 (25%)
3	0 (0%)	0 (0%)
12.hour		
1	17 (85%)	19 (95%)
2	3 (15%)	1 (5%)

Sedation score: 1= awake, 2=drowsy, 3=a sleep, easily rousable , 4= a sleep, hard to rouse . No significant between groups (p>0.05).

Table 3. Side effect and Patient satisfaction

	Group F (n=20)	Group D (n=20)	p
Nause vomiting	13 (%65)	3 (%15)*	0.03
Pruritis	10 (%50)	4 (%20)*	0.04
Patient satisfaction			
1- Completely dissatisfied	0 (%0)	0 (%0)	
2- Slightly dissatisfied	0 (%0)	0 (%0)	
3- significantly satisfied	5 (%25)	3 (%15)	0.45
4- Completely satisfied	15 (%75)	17 (%85)	0.50

n (%)* significant differences Group F

Table 4. PONV score and Use of Antiemetics

	(median/ min-max)	Group F	Group D
Post op	PONV	1.5 (1.3-1.6)	1.2 (1.1-1.3)
	Dizziness	0.4 (0.2-0.6)	0.2 (0.1-0.3)
	Antiemetics (amp)	0.1 (0.1-0.2)	1.1 (0.1-0.2)
1.hour	PONV	1.1(0.9-1.3)	1.0 (0.8-1.1)
	Dizziness	0.4(0.2-0.6)	0.2 (0.1-0.3)
	Antiemetics (amp)	0.1 (0.1-0.2)	0.1 (0.1-0.2)
4.hour	PONV	1.1 (0.9-1.3)	1.0 (0.8-1.1)
	Dizziness	0.4 (0.2-0.6)	0.2 (0.1-0.3)
	Antiemetics (amp)	0.1 (0.1-0.2)	0.1 (0.1-0.2)
8.hour	PONV	1.4 (1.2-1.6)	1.2(1.1-1.4)
	Dizziness	0.4 (0.2-0.6)	0.2 (0.1-0.3)
	Antiemetics (amp)	0.1 (0.1-0.2)	0.1 (0.1-0.2)
12.hour	PONV	1.5 (1.4-1.7)	0.3(0.2-0.4)*
	Dizziness	0.3 (0.2-0.4)	0.1 (0.1-0.2)
	Antiemetics (amp)	0.1 (0.1-0.2)	0.1 (0.1-0.2)
24.hour	PONV	1.0 (0.8-1.2)	0.2 (0.1-0.3)*
	Dizziness	0.2 (0.1-0.3)	0.1 (0.1-0.2)
	Antiemetics (amp)	0.1 (0.1-0.2)	0.1 (0.1-0.2)

The severity of side effects related to opioid was rated as: 0 = none, 1 = mild, 2 = moderate, 3 = severe and refractory to the treatment. * significant differences Group F(p =0.03).

were found to be similar (Table 1). Respiratory depression was not observed in either group (Table 2). Postoperative nausea and vomiting was significantly higher in Group F compared to Group D (p=0.03) (Table3). Nausea and vomiting occurred in 13 patients, in the Group F and in 3 patients in the Group D. Compared to Group F, PONV were reduced in Group D at 12 and 24 hours, postoperatively (p=0.03) (Table 4). No statistical difference was found between the two groups in the antiemetics used. Based on the incidence and severity of dizziness, no difference was found between the groups. Positive pruritus was significantly higher in Group F, compared to Group D (p=0.04)

Table 5. Fentanyl consumption

Time	Group F (n=20)	Group D (n=20)	p
2. hour	156,93±33,97	150,16±32,57	
min-max	120-189	118-184	**0,65**
4. hour	365,60 ±40,34	355,50 ±45,91	
min-max	332-410	315-390	**0,59**
8. hour	525,60 ± 47,07	500,16 ± 46,15	
min-max	486-560	467-548	**0,45**
12. hour	1000,0 ± 82,47	558,16±51,34 *	
min-max	957-1070	550-600	**0,001**
24. hour	1396,46±101,77	848,06±122,88 *	
min-max	1300-1480	730-858	**0,001**

Values are mean ± SD. * significant differences Group F (p= 0,001).

(Table 3). No significant difference was found between groups based on the VAS score (p= 0.07). Neither of the groups included any patient satisfaction ratings of "slightly dissatisfied" or "completely dissatisfied". In Group F, 15 patients were completely satisfied, compared with 17 in Group D, and no statistically significant difference was found between the two groups (p= 0.45) (Table 3). At 12 and 24 hours postoperatively, fentanyl consumption was significantly lower in Group D compared to Group F (p=0.001) (Table 5). No complications or side-effects attributable to Dexketoprofen trometamol were reported.

Discussion

Multimodal analgesia is the preferred method of managing pain caused by nociceptive and central stimulation. The goal of preemptive analgesia is to prevent pain perception by inhibiting peripheral and central sensitization developing due to pain stimulation [1]. The onset, continuation and recurrence stages of central sensitization should be blocked. Dexketoprofen, which is a NSAID agent, is preffered due to its quick absorbation and quick effect following administration [2]. Therefore, dexketoprofen was administered preemptively in this study.

Prior to abdominal hysterectomy, the fentanyl consumption of patients who were given, 50mg I.v of DKP preemptively and at 8 hours post-operatively, were 40% lower compared to patients who were only given fentanyl. There were no differences in VAS.

At 12 and 24-hours post-operatively, the incidence and severity of PONV was also lower in the group Group D, however, dizziness, use of additional analgesics and antiemetics did not differ significantly between the two groups. Nausea and vomiting was seen at a rate of 65% in the fentanyl-only group, compared with 15% in the Group D. Pruritus was seen in 50% of the Group F and 20% in Group D.

Various studies have reported that NSAIDs administered after surgery lead to better pain scores, and reduced opioid requirement by a third during the first and second days post-operatively [11]. Findings from recent research on early analgesic effects indicate a separate central mechanism [12,13]. As a result of reduced opioid consumption after surgery, a decrease in sedation, postoperative nausea, vomiting and pruritus; and increase in bowel function is seen which, in turn, lead to improved coordination and mobility in patients. Since dexketoprofen is thought to have an active role in the central nervous system, this drug is a great candidate, especially due to its involvement in nociception and in depressing a wind-up phenomenon [14]. Although animal data suggested that the preemptive administration of analgesic drugs may reduce postoperative analgesic requirements, the clinical evidence supporting this claim has been questioned by several investigative groups [15]. Reuben et al. reported that NSAIDs produced a "preemptive" effect when they were administered before versus after the surgical incision [16]. In a study by Tuncer et al. [2], which looked at patients undergoing abdominal hysterectomy, dexketoprofen administered peri-operatively was found to reduce the need for opioids by providing a significant analgesic benefit in patients. Miralles et al. [17] reported that, following total abdominal hysterectomy, administration of 50 mg of DKP at 8-hour intervals reduced morphine consumption by 44%, whereas 25 mg of DKP was not significant. Laitinen et al. [18] state that, compared to PCA monotherapy, PCC in combination with IV diclofenac reduced the requirement for fentanyl; however, there was no difference in the incidence of side-effects. In another study where Tuncer et al. used oral 25 mg DKP, no difference in nausea and vomiting was reported. Hanna et al. [19] report reduced incidence of nausea and vomiting, based on reduced morphine consumption, in a group where 50 mg IV of DKP was used.

When opioids are used, the incidence of PONV also increases and, compared to pain, patients consider PONV to be more stressful and unpleasant [9]. This is also shown by a study where 71% of patients gave PONV as the main reason for their poor perioperative experiences [10]. PONV may also increase recovery time, leading to an extended hospital stay, thus reducing patient satisfaction. In the present study, PONV score was significantly lower in the preemptive DKP group during the initial 12 and 24 hours post-operatively. However, no significant difference was observed between the groups based on the use of antiemetics.

NSAIDs reduce platelet aggregation and increase bleeding time. Reports in the literature indicate that the incidence of bleeding disorders associated with dexketoprofen is similar to that of hemorrhagic complications after a major surgical procedure [20]. When laboratory values are analyzed, including the bleeding time, coagulation parameters were not affected by the use of DKP and the results were not different from those obtained using a placebo [17]. Zabala et al. [21] reported a 35-year-old female patient being admitted to the hospital with fever, neutropenia, thrombocytopenia and liver damage, 10 days after oral DKP treatment. The symptoms improved after the drug use was discontinued, and were thought to be the result of an idiosyncratic hypersensitivity reaction. Latinien et al. [18] did not report any gastrointestinal irritation or bleeding problems in their group where DKP was used. In our study, no complaints regarding bleeding disorders or hypersensitivity occurred in the DKP group.

Conclusion: In patients who received 50 mg intravenous dexketoprofen trometamol prior to abdominal hysterectomy, we observed that fentanyl consumption decreased by 40%, analgesia quality increased and the incidence of side-effects decreased.

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