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Comparison of the Postoperative Analgesic Effectiveness and Side Effects of Intravenous Dexketoprofen Trometamol and Ibuprofen in Patients Undergoing Abdominal Hysterectomy: A Randomized, Double-Blind, Placebo-Controlled, Prospective Study

Abdominal Histerektomi Uygulanan Hastalarda İntravenöz Deksketoprofen Trometamol ve İbuprofenin Postoperatif Analjezik Etkinliğinin ve Yan Etkilerinin Karşılaştırılması: Randomize, Çift Kör, Plasebo Kontrollü Prospektif Çalışma

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ABSTRACT Objective: Postoperative pain prolongs recovery and hospital stay if not treated effectively. We aimed to compare the postoperative analgesic efficacy and side effects of intravenous dexketoprofen trometamol and ibuprofen in patients undergoing abdominal hysterectomy. **Material and Methods:** 90 patients aged 18-65 years, American Society of Anesthesiologists I-II, undergoing abdominal hysterectomy were randomly divided into 3 equal groups. At the transition to surgical closure, patients in ibuprofen group (Group I) received 400 mg of ibuprofen, patients in dexketoprofen group (Group D) received 50 mg of dexketoprofen (trometamol), and the patients in placebo group (Group P) received 100 ml of saline as infusion over 30 minutes. Patient controlled analgesia prepared with morphine was started in the postoperative period. Hemodynamic parameters, Visual Analogue Scale (VAS) scores, morphine consumption and possible side effects were recorded at postoperative 0, 10, 30 minutes and 1, 2, 6, 12, 24 hours. **Results:** Morphine comsumption, was observed as lower in Group I and Group D from the postoperative 6th hour compared to Group P, and in Group I it was decreased compared to Group D from the postoperative 6th hour ($p<0.005$). VAS scores, was found decreased in all measurements in Group I and in all measurements in Group D except the 6th hour compared to the placebo group ($p<0.05$). **Conclusion:** We concluded that both drugs reduce morphine consumption in the treatment of postoperative pain in abdominal hysterectomies, ibuprofen provides more effective postoperative analgesia than dexketoprofen (trometamol), and both drugs can be used safely in multimodal analgesia.

Keywords: Postoperative analgesia; dexketoprofen trometamol; ibuprofen; morphine

ÖZET Amaç: Postoperatif ağrı etkin şekilde tedavi edilmediği takdirde iyileşme ve hastanede yatış süresini uzatmaktadır. Abdominal histerektomi uygulanacak olan hastalarda intravenöz deksketoprofen (trometamol) ve ibuprofenin, postoperatif analjezik etkinliğini ve yan etkilerini karşılaştırmayı amaçladık. **Gereç ve Yöntemler:** Abdominal histerektomi uygulanacak 18-65 yaş arası, Amerikan Anestezistler Derneği I-II, 90 hasta randomize olarak 3 eşit gruba ayrıldı. Cerrahi kapamaya geçildiğinde; ibuprofen grubundaki (Grup I) hastalara 400 mg ibuprofen, deksketoprofen grubundaki (Grup D) hastalara 50 mg deksketoprofen (trometamol) ve plasebo grubundaki (Grup P) hastalara 100 ml serum fizyolojik, 30 dk'da infüzyon şeklinde uygulandı. Postoperatif dönemde tüm hastalara morfin ile hazırlanan hasta kontrollü analjezi başlandı. Hemodinamik parametreler, Görsel Analog Skala [Visual Analogue Scale (VAS)] değerleri, morfin tüketimi ve olası yan etkiler postoperatif 0, 10, 30. Dakikalarda ve 1, 2, 6, 12, 24. saatlerde kaydedildi. **Bulgular:** Morfin tüketiminin; Grup I ve Grup D'de postoperatif 6. saatten itibaren Grup P'ye göre düşük olduğu, Grup I'de ise postoperatif 6. saatten itibaren Grup D'ye göre azaldığı gözlendi ($p<0,05$). VAS değerlerinin; Grup I'de tüm ölçümlerde, Grup D'de ise 6. Saat hariç tüm ölçümlerde plasebo grubuna göre azaldığı, diğer tüm ölçümlerde Grup I'de düşük olduğu bulundu ($p<0,05$). **Sonuç:** Abdominal histerektomilerde postoperatif ağrı tedavisinde her iki ilacın da morfin tüketimini azalttığı, ibuprofenin deksketoprofen trometamole göre daha etkin bir postoperatif analjezi sağladığı ve her iki ilacın da multimodal analjezide güvenle kullanılabileceği sonucuna varılmıştır.

Anahtar Kelimeler: Postoperatif analjezi; deksketoprofen (trometamol); ibuprofen; morfin

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Postoperative pain is one of the most important events that contribute to the increase in postoperative morbidity and mortality.[1] Despite improved knowledge of advances in pharmacology and nociception, 31-37% of patients undergoing operation describe severe to unbearable postoperative pain, while 80% describe moderate to severe postoperative pain.[2] Failure to reduce postoperative pain causes significant morbidities such as impaired gastrointestinal activity, pulmonary and cardiac complications, delayed wound healing and thromboembolic events. Fast and effective pain treatment both shortens the hospitalization period and enables patients to return to their daily activities faster. Many drugs and methods are preferred to reduce postoperative pain. Multimodal analgesia method, which acts by different mechanisms and combines different analgesic drugs, is recommended in the relief of postoperative pain. With this method, much lower drug doses are used, while less side effects occur by utilizing the additive effects of analgesics, an effective analgesia is provided.[1,3]

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in multimodal postoperative pain management. Dexketoprofen (trometamol) (Deva, Turkey) is produced as a pure water-soluble formulation of the active S-enantiomer of ketoprofen, a potent prostaglandin synthesis inhibitor.[4] Dexketoprofen (trometamol), a centrally acting NSAID, is frequently preferred due to its low gastrointestinal side effects and rapid onset of action.[5,6] Ibuprofen (Polifarma, Turkey) is a non-specific inhibitor of cyclooxygenase enzymes and is a propionic acid derivative NSAID.[7] The oral form of ibuprofen, which has antipyretic, anti-inflammatory and analgesic effects, has been widely used in recent years. The parenteral form of ibuprofen has been used in the USA since 2009 to treat mild to moderate pain and is also used in combination with opioids to treat severe pain.[8] Although there are not enough studies on intravenous ibuprofen yet, it has been shown that it can be used and effective in reducing postoperative pain.[9]

In this randomized, double-blind, placebo-controlled, prospective study, we aimed to compare the postoperative analgesic efficacy and side effects of intravenous (iv) dexketoprofen (trometamol) and ibuprofen in patients undergoing abdominal hysterectomy.

MATERIAL AND METHODS

STUDY DESIGN

After the approval of Erciyes University Clinical Research Ethics Committee, dated November 24, 2017 (no: 2017/540), this randomized, double-blind, placebo-controlled, prospective study was conducted in Erciyes University Gevher Nesibe Research and Training Hospital Department of Anesthesiology and Reanimation, Gynecology and Obstetrics operating room. This study was carried out in accordance with the Principles of the Declaration of Helsinki.

STUDY POPULATION

American Society of Anesthesiologists I-II group patients, aged between 18 and 65 years, who would undergo elective total abdominal hysterectomy operation were included in this double-blind study, in which treatment assignment was blinded.

Patients with renal dysfunction, liver dysfunction, history of gastrointestinal bleeding, history of peptic ulcer, use of anticoagulants except prophylactic subcutaneous heparin use, history of long-term NSAID use, opioid tolerance or addiction, Body Mass Index >30 kg/m^2, patients who were uncooperative for pain assessment and allergic (to study drugs) were excluded from the study. In total 96 patients screened for this study, 90 adult patients gave written informed consent were enrolled in the study (6 patients declined to participate).

RANDOMIZATION

Patients who met the criteria for inclusion in the study were identified by interviewing the relevant surgical team. In order to prevent selection bias that may occur in the study and to increase the validity of the study, the patients were divided into 3 groups using the closed opaque envelope method after obtaining informed consent. Study groups were determined as Dexketoprofen (trometamol) administered group (Group D), ibuprofen administered group (Group I), and placebo administered group (Group P). The randomization process was conducted by people

other than the researchers and was not involved in any other part of the study. The researchers were unaware of the randomization process. Anesthesia management, monitoring and recording of parameters were performed by another researcher, unaware of the group distribution and blinded to the study, other than the one administering the drugs.

PREOPERATIVE PREPARATION AND INTRAOPERATIVE MANAGEMENT

All patients were interviewed 24 hours before operation and informed about patient-controlled analgesia (PCA). After written informed consent was obtained from all patients, information was given about the study protocol, the PCA device and the Visual Analogue Scale (VAS).

All patients were taken to the operating table without sedation and with at least 8 hours of fasting. All patients were given 5 mL/kg crystalloid fluid preoperatively and were maintained with crystalloid fluid infusion (8-10 mL/kg/hour) throughout the operation. Routine nausea-vomiting prophylaxis was administered with granisetron (Deva, Turkey). During the operation, noninvasive blood pressure, peripheral oxygen saturation (SpO_2) and electrocardiography parameters of all patients were monitored and all parameters were recorded at 5-minute intervals. After preoxygenation with 100% O_2, iv propofol (Polifarma, Turkey) 1.5-2 mg/kg, iv fentanyl (Polifarma, Turkey) 1 µg/kg and iv rocuronium (Merck Sharp Dohme, Holland) 0.6 mg/kg were administered to all patients for anesthesia induction. As anesthesia maintenance, a mixture of oxygen and air (50% O2/50% air) and 2-3% sevoflurane (Baxter, Turkey) was administered. In terms of muscle relaxation, rocuronium 0.1 mg/kg was added when necessary.

At the transition to surgical closure; 50 mg of dexketoprofen (trometamol) (Arveles®, Menarini International, Florence, Italy) in 100 ml of saline administered in Group D, 400 mg of ibuprofen (Intrafen®, Gen Ilac, İstanbul, Türkiye) in 100 ml of saline administered in Group I, and 100 ml of saline administered in Group P as infusion over 30 minutes. In order to prevent the drugs from being recognized, the study drugs were prepared in a black case by the anesthesia nurse and administered by a member of the research team. The researchers (collect postoperative data), surgical team and the patient were blinded to the study drugs. 0.02 mg/kg atropine and 0.04 mg/kg neostigmine were given intravenously for muscle relaxation antagonism at the end of the surgery. After extubation, all patients were transferred to the postoperative care unit (PACU).

POSTOPERATIVE ANALGESIA MANAGEMENT

Postoperative pain severity was assessed by asking the patient a VAS score from 0 to 10 (0=no pain and 10=most pain). In the PACU, a PCA device containing 0.5 mg/mL morphine (Haver, Turkey) was connected to all patients and iv analgesia was administered 24 hours. When the VAS score was >3 in the PACU, PCA was initiated to all three groups, with a bolus dose of 1 mg, a lockout time of 15 minutes, and no basal infusion. Patients were followed in the PACU until the postoperative Aldrete recovery score was ≥9 (Table 1), and then in the ward. The severity of pain of the patients visited in the ward was evaluated with the VAS score.

Demographic and clinical characteristics of patients, and time to reach Aldrete recovery score ≥9 were recorded. Hemodynamic parameters, morphine consumption, VAS scores and possible side effects were also recorded at postoperative 0, 10, 30 minutes and 1, 2, 6, 12, 24 hours.

TABLE 1: Aldrete recovery score.

Assessment items	Condition	Grade
Activity, able to move, voluntarily or on command	4 extremities	2
	2 extremities	1
	No	0
Respiration	Able to breathe deeply and cough freely	2
	Dyspnea, shallow or limited breathing	1
	Apnea	0
Consciousness	Fully awake	2
	Arousable on calling	1
	Not responding	0
Circulation (Blood pressure)	±20% of pre-anesthesia level	2
	±20% to 49% of pre-anesthesia level	1
	±50% of pre-anesthesia level	0
Skin color	Normal	2
	Pale, dusky, blotchy, jaundiced, other	1
	Cyanotic	0

STATISTICAL ANALYSIS

Mean, standard deviation, median values were given in descriptive statistics for continuous data, and number percentage values were given in discrete data. The Shapiro-Wilk test was used to examine the conformity of continuous data with normal distribution. Kruskal-Wallis test was applied for the comparisons of the median values. For statistical evaluation of quantitative variables with normal distribution, t-test was used; the Wilcoxon test was used for non-quantitative variables. Statistical evaluation of qualitative variables was performed by Pearson chi-square analysis and Fisher's exact chi-square analysis. The data were analyzed using IBM SPSS for Windows version 20 (IBM Corp, Armonk, NY, USA). A value of $p<0.05$ was considered statistically significant.

RESULTS

All study groups were compared according to demographic data, clinical parameters and time to reach Aldrete recovery score, and the characteristics were found to be similar (Table 2). Heart rate and mean blood pressure were significantly lower in study groups than in Group P at all measurement times ($p<0.05$), as expected. Additionally, SpO_2 were similar between all study groups at all measurement times.

As presented in Table 3, it was found that VAS scores decreased in all measurements in Group I ($p<0.05$), and in all measurements in Group D except the 6th hour compared to Group P ($p<0.05$), when the study groups were compared, it was similar only at the 12th hour, while it was lower in Group I in all other measurements (Figure 1). VAS scores of the Group I recorded for 24 hours, except for the 12th hour, were found to be significantly lower than those of group D and group P ($p<0.05$).

The morphine consumption was similar in all groups until the second hour (Table 4). While the total morphine consumption recorded at the 6th, 12th and 24th hours in Group D was statistically

TABLE 2: Patient characteristics.

Variables	Group D	Group I	Group P	p value
Age, years, $\bar{X}$±SD	51.70±9.91	52.13±5.87	52.13±6.77	0.510[a]
Height, cm, $\bar{X}$±SD	163.87±4.83	162.33±5.38	161.90±3.55	0.170[a]
Weight, kg, $\bar{X}$±SD	80.73±10.54	79.10±12.40	79.50±10.18	0.580[a]
ASA class, 1/2, n (%)	17 (56.7)/13 (43.3)	14 (46.7)/ 16 (53.3)	14 (46.7)/16 (53.3)	0.670[b]
Time to reach Aldrete recovery score ≥9, minutes, $\bar{X}$±SD	23.00±1.44	22.10±3.05	23.30±1.93	0.780[a]

[a]Kruskal Wallis test; [b]Chi-square test; D: Dexketoprofen trometamol; I: Ibuprofen; P: Placebo; SD: Standard deviation; cm: Centimeter; kg: Kilogram; ASA: American Society of Anesthesiologists. A value of $p<0.05$ was considered statistically significant.

TABLE 3: Comparison of VAS scores at postoperative time points.

Variables	Group D	Group I	Group P	p value
At PACU	6.80±0.61	5.83±0.59	8.37±0.49	**<0.001*[a]**
10 minutes	6.80±0.61	5.76±0.63	8.10±0.31	**<0.001*[a]**
30 minutes	6.40±0.62	5.13±0.57	7.10±0.48	**<0.001*[a]**
1 hour	5.67±0.61	4.47±0.62	6.33±0.48	**<0.001*[a]**
2 hours	4.93±0.52	4.06±1.08	5.40±0.50	**<0.001*[a]**
6 hours	3.93±0.64	3.43±0.94	4.10±0.68	**0.007*[a]**
12 hours	2.40±0.67	2.06±0.83	2.93±0.64	**<0.001*[a]**
24 hours	1.06±0.83	0.43±0.50	2.17±0.38	**<0.001*[a]**

*Statistically significant difference between groups; [a]Kruskal-Wallis test; D: Dexketoprofen trometamol; I: Ibuprofen; P: Placebo; PACU: Postoperative care unit. Values are presented as mean±standart deviation; A value of $p<0.05$ was considered statistically significant.

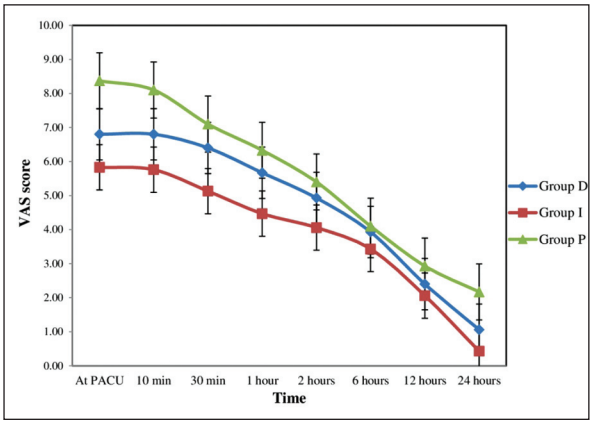

FIGURE 1: VAS scores of groups at postoperative time points
VAS: Visual analogue scale; PACU: Postoperative care unit; min: minutes; D: dexketoprofen trometamol; I: ibuprofen; P: placebo.

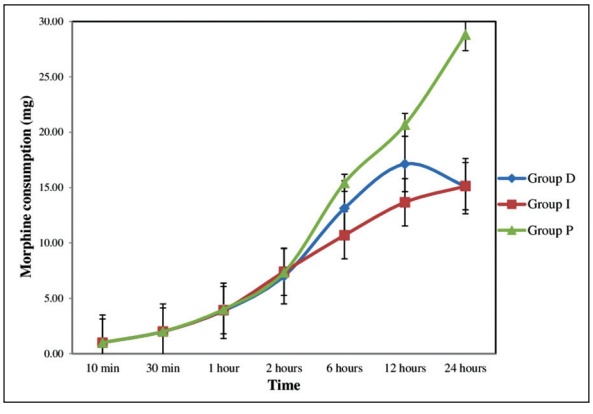

FIGURE 2: Morphine consumption of groups at postoperative time points
mg: milligram; min: minutes; D: dexketoprofen trometamol; I: ibuprofen; P: placebo.

TABLE 4: Comparison of morphine consumption at postoperative time points.

Variables	Group D	Group I	Group P	p value
15 minutes	1.00±0.0	1.00±0.0	1.00±0.0	1.00
30 minutes	2.00±0.0	2.00±0.0	2.00±0.0	1.00
1 hour	3.87±0.35	3.93±0.25	4.00±0.0	0.120
2 hours	7.00±1.02	7.40±0.93	7.33±0.88	0.181
6 hours	13.13±2.35	10.70±1.72	15.43±2.36	**<0.001**[*a]
12 hours	17.13±2.53	13.67±1.83	20.67±3.31	**<0.001**[*a]
24 hours	20.20±2.17	15.13±2.10	28.80±4.00	**<0.001**[*a]

*Statistically significant difference between groups; [a]Kruskal Wallis test. D: Dexketoprofen trometamol; I: Ibuprofen; P: Placebo; Values are presented as mean±standart deviation; A value of p<0.05 was considered statistically significant.

significantly decreased compared to group P (p<0.05), the total morphine consumption in Group I was statistically significantly lower compared to both group D and Group P (Figure 2).

TABLE 5: Comparison of side effects.

Variables	Group D	Group I	Group P	p value
Nausea, n (%)	13 (43.3)	10 (33.3)	13 (43.3)	0.659[b]
Vomiting, n (%)	9 (30)	6 (20)	5 (16.7)	0.434[b]
Shivering, n (%)	8 (26.7)	7 (23.3)	15 (50)	0.058[b]
Headache, n (%)	10 (33.3)	10 (33.3)	18 (60)	0.054[b]
Pruritus, n (%)	0	0	0	-
Dizziness, n (%)	0	3 (10)	1 (3.3)	0.160[b]
Dyspepsia, n (%)	0	0	0	-
Constipation, n (%)	7 (23.3)	0	18 (60)	**<0.001**[*b]

*Statistically significant difference between groups; [b]Chi-square test;
D: Dexketoprofen (trometamol); I: Ibuprofen; P: Placebo.
A value of p<0.05 was considered statistically significant.

Side effects were compared, it was seen that the number of patients with constipation in Group P was higher than the other 2 groups (p<0.05), and as shown in Table 5, other side effects (nausea, vomiting, shivering, headache, pruritus, dizziness, dyspepsia) were similar between the all groups.

DISCUSSION

In this randomized, double-blind, placebo-controlled, prospective study, we observed that ibuprofen provides more effective postoperative analgesia than dexketoprofen (trometamol), and both drugs can be used safely in multimodal analgesia.

Multimodal analgesia treatment is the combination of one or more analgesic agents and methods with different mechanisms of action. The purpose of this treatment strategy is to provide adequate analgesia with different analgesic drugs and to try to reduce the side effects and doses of the drugs used by taking advantage of the additive and synergistic effects of the drugs.[10] Another important consequence of why NSAIDs are preferred in multimodal analgesia is the decrease in postoperative pain levels.[11] Severe postoperative pain levels can be reduced using multimodal treatment strategies, and especially in major surgeries, opioids and NSAIDs are used together, thus increasing analgesic effectiveness. We also preferred the multimodal analgesia treatment strategy in our study.

The ibuprofen (iv form) has been assessed in many studies in the treatment of postoperative pain, and although there are insufficient number of studies on the use of ibuprofen, these studies report that iv ibuprofen can be used safely as a part of multimodal analgesia.[12-17] In a randomized controlled study conducted by Southworth et al. in 406 patients undergoing abdominal and orthopedic operation, a significant reduction in opioid consumption and lower pain levels were observed in iv ibuprofen group compared to placebo.[14] Again, in a multicenter, placebo-controlled study conducted by Gago Martínez et al. in 206 patients undergoing abdominal and orthopedic operation, it was reported that iv ibuprofen provided a significant reduction in opioid consumption and was accompanied by lower pain levels.[15] In their study of 319 patients undergoing abdominal hysterectomy, Kroll et al. found that iv ibuprofen provided a significant reduction in opioid consumption and pain levels compared to the placebo group.[16] In a study conducted by Singla et al. in 185 adult patients undergoing elective orthopedic operation, they observed a significant reduction in pain levels with iv ibuprofen and a reduction in opioid consumption compared to placebo.[17] In our study, total morphine consumption was found to be significantly lower in the ibuprofen group compared to the dexketoprofen (trometamol) and placebo groups.

Dexketoprofen (trometamol) is one of the frequently preferred agents in the treatment of postoperative pain. Many studies have been conducted investigating its effectiveness and it has been reported that it significantly reduces opioid consumption.[18-21] Karaman et al. in their study on 56 patients who undergoing major gynecological operation, reported that dexketoprofen (trometamol) reduced opioid consumption in the postoperative period and provided effective analgesia.[20] Similarly, Tuncer et al., in their study on patients who undergoing abdominal hysterectomy, stated that pain scores and opioid consumption were lower in the dexketoprofen (trometamol) administered group.[21] In our study, total morphine consumption and pain scores were found to be significantly lower in the dexketoprofen group compared to the placebo group.

In their study on 50 patients undergoing septorhinoplasty, Gozeler et al. administered ibuprofen preemptively and emphasized that postoperative pain scores were lower in the ibuprofen group than in the placebo group.[22] In their study on 60 patients undergoing cholecystectomy, Ahiskalioglu et al. observed that ibuprofen administered preemptively reduced opioid consumption.[23] In another study, Çelik et al. compared the effectiveness of ibuprofen and acetaminophen. In their study on 150 patients undergoing rhinoplasty, they administered the drugs preemptively and emphasized that ibuprofen provided more effective postoperative analgesia than acetaminophen.[24] In our study, we administered agents as part of our multimodal analgesia strategy when surgical closure was initiated and compared ibuprofen with dexketoprofen (trometamol). Studies comparing the analgesic effectiveness of ibuprofen and dexketoprofen (trometamol) are quite limited in the literature. In their study on 76 patients who undergoing septorhinoplasty, Kemal et al. administered ibuprofen and dexketoprofen (trometamol) preemptively and stated that both drugs had similar postoperative analgesic effectiveness.[25] According to the results of our study, both ibuprofen and dexketoprofen (trometamol) reduced total morphine consumption; however, ibuprofen was found to be superior to dexketoprofen (trometamol) in providing more effective postoperative analgesia. Therefore, we emphasize that both drugs can be used safely in multimodal analgesia treatment.

NSAIDs reduce or reverse peripheral sensitization by inhibiting prostaglandin synthesis. It also affects central sensitization by suppressing prostonoid formation in the brain and spinal cord, thus providing analgesic effects.[26,27] In our study, we explain the lower VAS scores in the ibuprofen group compared to the dexketoprofen (trometamol) and placebo groups with the peripheral and high central nervous system effects of ibuprofen.

It has been reported that the reduction in opioid consumption varies with different types of NSAIDs compared to placebo, and their effectiveness may

also be different.[11] Drug-related side effects are one of the most important reasons why opioids are not preferred.[28] In our study, total morphine consumption was found to be significantly lower in the ibuprofen group compared to other study groups. A safety analysis study by Southworth et al. emphasized that ibuprofen can be safely administered perioperatively as a component of multimodal pain management and suggested that it was not associated with a significant increase in side effects compared to placebo.[27] In our study, although constipation was significantly higher in the placebo group due to opioid use, no statistically significant difference was found between all groups in terms of other side effects. Additionally, no patient had constipation in the ibuprofen group. We believe that the lower total morphine consumption in the ibuprofen group may have led to earlier bowel function.

Our study has some limitations. First, our sample size was not sufficient to evaluate opioid-related side effects. Since the primer outcome of our study is to reduce total morphine consumption, our sample size was determined according to this purpose. We believe that further studies with larger sample sizes are needed. Secondly, in our study, we used ibuprofen, which has 2 forms (400 mg and 800 mg), at a dose of 400 mg. A different side effect profile and different results may occur with ibuprofen at the 800 mg dose. Finally, length of hospital stay was not evaluated in our study.

CONCLUSION

In conclusion, our study showed that ibuprofen provides more effective postoperative analgesia than dexketoprofen (trometamol) and both drugs can be used safely as part of a multimodal analgesia treatment strategy.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Erdem Bağcı, Gülen Güler;* ***Design:*** *Erdem Bağcı, Gülen Güler, Kemal Demirtaş;* ***Control/Supervision:*** *Gülen Güler;* ***Data Collection and/or Processing:*** *Erdem Bağcı, Gülen Güler, Kemal Demirtaş;* ***Analysis and/or Interpretation:*** *Erdem Bağcı, Kemal Demirtaş;* ***Literature Review:*** *Erdem Bağcı, Kemal Demirtaş;* ***Writing the Article:*** *Erdem Bağcı, Gülen Güler, Kemal Demirtaş;* ***Critical Review:*** *Gülen Güler;* ***References and Fundings:*** *Erdem Bağcı, Kemal Demirtaş;* ***Materials:*** *Erdem Bağcı, Kemal Demirtaş.*

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