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Orijinal Makale **Yağan ve ark.**

Propofol Enjeksiyon Ağrısının Önlenmesinde Deksketoprofen ve Tenoksikamın Etkileri

The Effect of Intravenous Dexketoprofen and Tenoxicam on Propofol Injection Pain

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Özet

Amaç: Çalışmamızın amacı propofol enjeksiyon ağrısının önlenmesinde tenoksikam ve deksketoprofenin etkinliğini araştırmaktır.Metod: Çalışmaya 20-60 yaş arası 150 hastanın dahil edilmesi planlandı. Hastalar randomize olarak 3 gruba ayrıldı. Genel anestezi indüksiyonu için iv olarak propofol uygulanmasından 2 dk önce hastalara; Grup I'de 2 mL salin, Grup II'de 20 mg (2mL) tenoksikam, Grup III'te ise 50 mg (2mL) deksketoprofen uygulandı. Hesaplanan propofol dozunun 4'te 1'inin uygulanması sonrası enjeksiyon ağrısı 4 puanlı verbal derecelendirme skalası (VRS) ve nümerik değerlendirme skalası (NRS) ile değerlendirildi. Bulgular: Deksketoprofen grubu, çalışma ilacı uygulaması esnasında hastaların şiddetli ağrı duyması nedeniyle 18. hastada sonlandırıldı. Toplam 118 hastanın verileri değerlendirildi. Propofol enjeksiyon ağrısı sıklığı salin grubunda %76, tenoksikam grubunda ise %38 idi ve fark istatistiksel olarak anlamlıydı (p<0,01). NRS skorları salin grubunda 3,1±2,2, tenoksikam grubunda 1,7±1,7 ve deksketoprofen grubunda 1,9±1,5 idi ve salin grubunda tenoksikam ve deksketoprofen grubu ile karşılaştırıldığında istatistiksel olarak anlamlı şekilde yüksekti (sırasıyla p<0,01 ve p<0,05). Sonuç: Çalışmamız sonucunda 20 mg iv tenoxicam ön tedavisinin, propofol enjeksiyon ağrısını azaltmada etkili olduğunu tespit ettik.

Anahtar kelimeler: Deksketoprofen, enjeksiyon ağrısı, propofol, tenoksikam

Abstract

Background and Objectives: The aim of our study is to research the efficacy of tenoxicam and dexketoprofen in preventing propofol injection pain. Methods: The study included 150 patients aged from 20 to 60 years. The patients were randomly divided into 3 groups. Two minutes before iv propofol administration for induction of general anesthesia patients in Group I were given 2 mL saline, patients in Group II were given 20 mg (2 mL) tenoxicam and patients in Group III were given 50 mg (2 mL) dexketoprofen. After administering 1 quarter of the calculated propofol dose injection pain severity was assessed using a four-point verbal rating scale (VRS) and numeric rating scale (NRS).Results: Due to pain felt during administration of the study medication in the dexketoprofen group, the study was terminated after 18 patients. The data from 118 patients were assessed. The incidence of propofol injection pain in the saline group was 76%, while this was 38% in the tenoxicam group and the difference was statistically significant (p<0.01). NRS score was 3.1±2.2 in the saline group, 1.7±1.7 in the tenoxicam group and 1.9±1.5 in the dexketoprofen group and it was statistically significantly higher in the saline group compared to the tenoxicam and dexketoprofen groups (p<0.01 and p<0.05 respectively). Conclusions: At the end of our study we identified that 20 mg iv tenoxicam pretreatment was effective in reducing propofol injection pain.

Key words: Dexketoprofen, injection pain, propofol, tenoxicam

Introduction

Propofol is commonly used for the induction and maintenance of general anesthesia, although it causes considerable pain discomfort or pain during intravenous (iv) injection. The incidence of injection pain has been shown to variablity between 28% and 90% in adults (1). Various factors, including the site of injection, speed of injection, vein size, aqueous phase propofol concentration, propofol temperature, blood buffering, gender, menstrual phase in woman and the concomitant use of various drugs, appear to influence this pain (2,3).

Although the underlying mechanism or etiology of pain induced by propofol injection is not clear, activation of the kallikrein-kinin system has been implicated (4). Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to diminish prostaglandin synthesis and inhibit kinin cascade, thereby reducing pain on injection of propofol (5).

Various NSAIDs such a acetaminophen, (6) aspirin, (7) ketorolac (8) have been used to reduce the pain during propofol injection. Dexketoprofen is a potent inhibitor of prostaglandin synthesis in vitro and demonstrates good analgesic activity compared with other NSAIDs (9). Tenoxicam is a NSAID that produces analgesic effect by non-selective cyclo-oxygenase (COX) inhibition. Although dexketoprofen and tenoxicam are effective for many types of pain and are commonly used analgesics, there wasn’t any studies to date have looked at the dexketoprofen and tenoxicam for the pretreatment of pain on injection of propofol in literature.

The hypothesis of our study is that, similar to other NSAIDs, dexketoprofen and tenoxicam will be effective to relieve pain from propofol injection. Therefore, in this study designed to test this hypothesis, we

aimed to evaluate the effect of iv dexketoprofen and tenoxicam for prevention of propofol-induced pain during induction of anaesthesia. The primary endpoint of this study was the absence of pain and pain severity during propofol injection.

Material and Methods

This prospective, randomized, double-blind, placebo-controlled study was approved by Ethics Committee of Ondokuz Mayıs University (2014/779), and it was registered at ClinicalTrials.gov (NCT02285972) and conducted in accordance with the Declaration of Helsinki. After obtained written informed consent, 150 patients aged 20–60 years, ASA physical status I or II, and undergoing general anaesthesia were included in this study. Exclusion criteria included; patients with vascular diseases, allergic diseases or sensitivity to study drugs, use of analgesics or sedative drugs within 24 hours before surgery, patients requiring a rapid sequence induction, history of drug or alcohol abuse, pregnancy, communication difficulty, psychiatric and neurological disorders, refusal to participate and patients already participating in another study.

Patients were randomly allocated to one of the three groups of 50 each using a computer generated sequence of numbers and a sealed envelope technique. The study medications were prepared by anesthesiologists (SA and AG) not included in the study in injectors with the same volume and wrapped in foil to prevent the color of the fluid from being observed. The study was completed in a double blind manner by ensuring the patient and the researcher (ÖY and TM) evaluating the injection pain was not aware of the medication used.

None of the patients received premedication. In the operating room patient was monitored with electrocardiogram, noninvasive arterial blood pressure and pulse oximeter (Mindray, BeneView T8, Shenzhen, P. R. China). A 20-gauge catheter was inserted into the dorsum of the hand and lactated Ringer's solution was infused at 100 mL h-1. After 5 min, the patients were pretreated over a period of 10 s with one of the study solutions; 2 mL of saline in Group I, 20 mg tenoxicam (Oksamen L 20 mg flacon, MN Ilac, Istanbul, Turkey) diluated with saline to 2 mL in Group II, or 2 mL 50 mg dexketoprofen (Arveles 50 mg 2 mL ampoule, Ufsa Ilac, Istanbul, Turkey) in Group III.

After 2 min, one-fourth of the total calculated dose (2.5 mg kg-1) of propofol (Propofol-Lipuro 1% 10 mg mL-1, B Braun, Melsungen, Germany) was delivered through the iv line over a period of 5 s, followed again by free flow of the lactated Ringer's solution. Ten seconds following the injection of propofol, the subjects were asked a standard question about pain on injection (Are you having pain at your iv site?) and their response was noted. Injection pain severity was assessed using the following four-point verbal rating scale (VRS): 0 = no pain; 1 = mild pain (pain reported only in response to questioning and without behavioral signs); 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign, or pain reported spontaneously without questioning); and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears)(10) and numeric rating scale (NRS): 0 (no pain) to 10 (worst pain imaginable). Thereafter, induction of anaesthesia continued with iv fentanyl 1-2 μg kg-1

followed by the remainder of the calculated dose of propofol, and rocuronium 0.6 mg kg-1 to facilitate endotracheal intubation. Within 24 h after the operation, the injection site was checked for pain, oedema, or allergic reaction by investigators.

Power analysis

The study sample size was calculated based on a hypothesized 65 % incidence of propofol injection pain with no intravenous pretreatment and a 35 % incidence with treatment.(2) With these assumptions, 48 patients were required each group to detect a significant difference with 80 % power and 5% significance ($\alpha = 0.05$, $\beta = 0.80$) in two way significant interactions (Minitab 13.1 Inc. State College PA, USA). We planned to include 50 patients in each groups in this study to allow for dropouts.

Statistical analysis

Statistical analysis was performed using the program SPSS 20.0 (IBM SPSS Statistics, Chicago, IL, USA). Continuous variables are presented as mean ± SD, categorical data are presented as number (%). Mann-Whitney U test were used to assess the demographic data and pain severity scores. ASA physical status, gender and incidence of pain were assessed with the chi-square test. Value of $p \leq 0.05$ was considered as a statistically significant.

Results

A total of 118 patients were enrolled in the study (Figure 1). In Group III as the patients felt pain during administration of the study medication (dexketoprofen), for ethical reasons the study was ended after the 18th patient.

There were no significant differences in age, weight, gender and ASA physical status among the groups ($P>0.05$, Table 1). The overall incidence of pain during iv injection of propofol in the three groups is shown in Table 2. The incidence of propofol injection pain was 76% (38 of 50) in the saline group, 38% (19 of 50) in the tenoxicam group and 56% (10 of 18) in the dexketoprofen group. Data analyses showed that tenoxicam pretreatment was reduced propofol associated pain when compared to saline group ($P<0.01$). In addition, NRS scores was 3.1±2.2 in the saline group, 1.7±1.7 in the tenoxicam group and 1.9±1,5 in the dexketoprofen group and it was statistically significantly higher in the saline group more than tenoxicam and dexketoprofen groups ($P<0.01$ and $P<0.05$ respectively, Figure 2).

No complications, such as pain, oedema, wheal or flare response, were observed at the injection site within the first 24 h after the operation.

Table 1. Patients characteristics. Data are presented as mean ± SD or frequencies.

	Group I saline n = 50	**Group II** tenoxicam n = 50	**Group III** dexketoprofen n = 18
Age (yr)	39.12 ± 8.70	37.58 ± 11.85	36.89 ± 13.37
Weight (kg)	68.10 ± 9.35	65.84 ± 9.18	70.61 ± 9.79
Gender (F / M)	23 / 27	26 / 24	9 / 9
ASA I / II	30 / 20	27 / 23	11 / 7

F/M: Female / Male, ASA: American Society of Anesthesiologist

Table 2. Incidence and severity of pain during iv injection of propofol. Data are presented as frequencies (%).

	Group I saline n = 50	**Group II** tenoxicam n = 50	**Group III** dexketoprofen n = 18
No pain	12 (24%)	31 (62%)*	8 (44%)
Mild pain	18 (36%)	11 (22%)	7 (39%)
Moderate pain	15 (30%)	7 (14%)	3 (17%)
Severe pain	5 (10%)	1 (2%)	0 (0%)
Total pain	38 (76%)	19 (38%)*	10 (56%)

*: $P<0.05$; Chi Square test; Group II vs I.

Figure 1. CONSORT flow diagram of this randomized trial.(11)

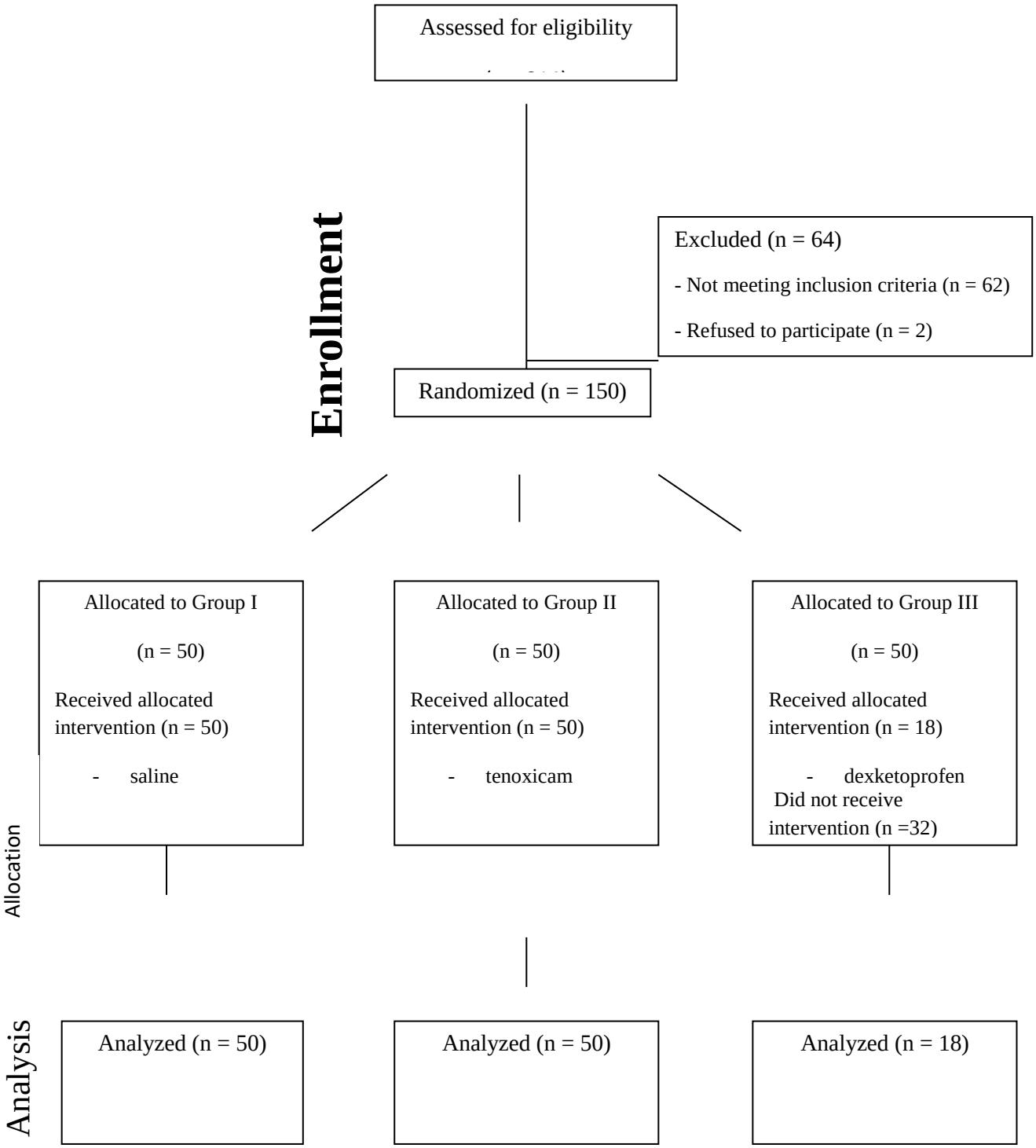
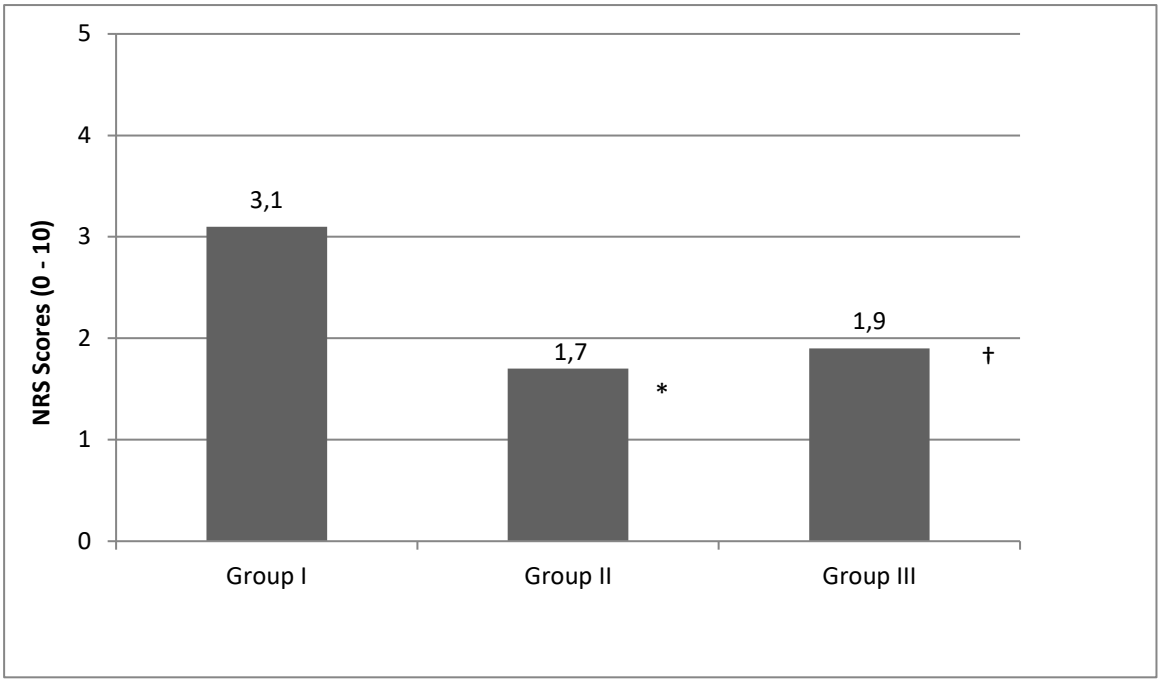


Figure 2. Numeric rating scale (NRS) of patients with pain during injection of propofol. 0: no pain, to 10: worst pain imaginable.



*: p<0.05; Mann Whitney U test; Group II vs I. †: p<0.05; Mann Whitney U test; Group III vs I.

Discussion

The main finding of this study is that iv pretreatment with tenoxicam reduced the pain during iv propofol injection. The results also indicate that dexketoprofen causes pain during intravenous injection. The mechanism by which propofol causes pain on injection remains unclear. It is reported that activation of the kallikrein-kinin cascade is responsible for pain felt during propofol injection (12). The lipid solvent for propofol activates the plasma kallikrein–kinin system which results in bradykinin production that increases local vein permeability and dilation. This suggestion was supported by Iwama et al (13). who demonstrated that the pretreatment with kallikrein inhibitor inhibited the propofol injection pain.

A variety of techniques are used to prevent or reduce propofol injection pain including diluting propofol, cooling or heating the drug, using larger vein for injection, and pharmacological pretreatment. With this aim, many medications from different groups have been studied including a variety of doses of lidocaine, (1,14) opioids, (15) ondansetron, (16) dexmedetomidine,(17) magnesium, (10) and metoclopramide (18). Lidocaine, administered before or with propofol injections, still appears to be the most effective method to relieve injection pain (6,19). In the literature there are a variety of rates reported for incidence of propofol injection pain with lidocaine; Canbay et al.6 reported 8% while Pang et al (20). reported 11%. However, some studies have reported higher incidences such as 18% and 42% (21,22).

There are studies in the literature on a variety of NSAIDs used to prevent propofol injections pain. Some of these medications include paracetamol, (6,23) ketorolac,(24) flurbiprofen, (25) parecoxib, (26) and diclofenac (27). In a study using different doses of iv paracetamol to prevent propofol injection pain, Borazan et al (23). identified that all groups had reduced injection pain compared to the control group. They reported that iv 2 mg kg-1 paracetamol was more effective than 0.5 mg kg-1 lidocaine in preventing propofol injection pain. They stated that this result may be due to the constructive effect of prostaglandin synthesis inhibition by paracetamol.

Ketorolac, preventing prostoglandin production through COX inhibition, is one of the NSAIDs used to prevent propofol injection pain. Huang et al (8). in a study researching the effects of ketorolac on propofol injection pain, reported that pretreatment with iv ketorolac when used without a tourniquet at high doses, or with a tourniquet at low doses, was effective at preventing propofol injection pain. They stated that the propofol injection pain mechanism might be along the COX pathway.

Yull et al (24). in a study of venous occlusion found that ketorolac was effective at reducing propofol injection pain. They reported that propofol injection pain may be related to local kininogen release and that NSAIDs might be effective at reducing this pain. There are studies of the effects of NSAIDs on propofol injection pain with different results. Karasawa et al (25). found flurbiprofen axetil had no effect, while Smith et al (28). reported that 10 mg iv ketorolac did not reduce propofol injection pain. Further, they mentioned that NSAIDs may have irritant effects during iv administration. Because of this effect Karasawa et al (25) used a NSAID prodrug in their studies.

Dexketoprofen is an active enantiomer with potential for more rapid onset of effect, more potent and fewer side effects than racemic ketoprofen (29). There are many studies showing its efficacy for preemptive analgesia with many surgery types in oral or parenteral administration. It is known that racemic ketoprofen causes venous irritation when administered with iv injection. Sjövall et al (30) compared dexketoprofen and racemic ketoprofen in terms of iv injection pain and found that dexketoprofen caused less pain. Of 210 patients, 151 (75%) felt pain after dexketoprofen administration and the rate of patients reporting moderate or severe pain was 20%. In our study, we had to stop after the 18th patient in the group given iv dexketoprofen, Group III, as patients felt pain during administration of the study drug. As long as our study continued, iv administration of dexketoprofen caused pain; however it did reduce the severity of propofol injection pain felt by patients.

Tenoxicam is one of the oxicam class of NSAIDs, acting in part through the non-selective inhibition of COX-1 and -2 to produce analgesic and antipyretic effects (31). When compared to other NSAIDs it is reported to have some advantages for elderly patients with renal or hepatic failure (32). Additionally it is thought that the low tissue penetration reduces side effects of this medication (33). Tenoxicam is produced as 20 mg oral tablets, 20 mg suppositories and 20 or 40 mg powders for injection (iv or intramuscular) and is used in many painful situations such as postoperative pain,

endodontic therapy, and arthritis (34,35). In our first study in the literature, we found iv administered tenoxicam effective in preventing propofol injection pain. The propofol injection pain incidence among patients given pretreatment with tenoxicam was 38%, while this rate was 76% in the group not given treatment. At the same time in patients feeling pain during injection evaluated with NRS, the severity of pain was significantly low in the tenoxicam group compared to the control group (3.1 compared to 1.7). When we consider that we did not encounter any side effects during our study, we believe that tenoxicam may be used to prevent and/or reduce propofol injection pain.

In our study the propofol injection pain incidence was 76% in the control group. This result, though within the range reported in previous studies, appears to be slightly high which we consider might be due to the injection location on the back of the hand. It is reported that propofol injection pain is linked to the diameter of the vein used for injection (4). For example, Karasawa et al. used the cephalic vein in the forearm and identified propofol injection pain incidence of 50% in the control group (25).

The most important limitation of our study is that the target number of patients could not be reached in the dexketoprofen group due to ceasing the study for ethical reasons because of pain felt by cases. Though reported at lower rates for tenoxicam and dexketoprofen, gastric intolerance is a well-known side effect of NSAIDs (9,32). However, in our study we did not encounter this situation which may be due to our patient numbers not being sufficient to observe side effects. Though lidocaine still appears to be the most effective medication o prevent propofol injection pain, ethical rules in our country does not permit studies of lidocaine used for this reason, so another limitation is that we could not compare with lidocaine.

At the end of our study we identified that 20 mg iv tenoxicam pretreatment is effective in reducing propofol injection pain. We believe studies using different doses and conditions (for example, with venous occlusion or different waiting periods) are required.

Foot Note: This study was presented as a poster at Turkish Anesthesiology and Reanimation Association 49th National Congress in Antalya in 2015.

Conflict of Interest: None.

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Informed Consent: Written informed consent was obtained from patients who participated in.

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