

## Lornoxicam use to reduce the pain associated with propofol injection

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### ABSTRACT

**Aim:** To investigate the efficacy of lornoxicam in the prevention of the pain associated with propofol injection.

**Material and method:** Approval for this study was granted by the ethics committee of our hospital. Using a computer randomisation software, 120 patients undergoing elective surgery were assigned to four equal groups. In Group I (control group), immediately before anaesthesia induction, 10 ml of isotonic 0.9% NaCl solution (placebo) was administered intravenously (IV). In Groups II, III and IV, the same injection contained 2 mg, 4 mg and 8 mg of lornoxicam respectively. A tourniquet was then applied to the forearm for two minutes. Pain evaluation was made using a verbal pain score.

**Results:** Differences in pain severity scores were statistically significant between Groups I and II, Groups I and III, Groups I and IV and between Groups II and III ( $p < 0.05$ ). However, no significant difference was determined between Groups III and IV ( $p = 0.401$ ).

**Conclusion:** In all groups administered with lornoxicam, there was a significant reduction in the severity of pain associated with propofol injection, in comparison with the control group. Maximum effect is obtained with a dose of 4 mg.

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## Introduction

Propofol (2,6-diisopropylphenol), a widely used intravenous (IV) anaesthetic, was developed in the 1970s from phenol derivatives [1,2]. Just as propofol is used for the induction and maintenance of anaesthesia, it is also often used outside operating theatres for sedation. As propofol has a rapid onset time and early recovery, it is close to ideal as an anaesthetic agent [3,4]. The most frequently seen side-effect of its use is injection pain and associated patient discomfort [5]. The incidence of pain and discomfort during propofol injection has been reported at rates between 28% and 90% [6]. Many methods have been used to reduce this pain including the addition of lidocaine to propofol, adjusting the pH of the propofol emulsion, prior administration of alfentanil, remifentanil, ketamine, metoclopramide, nafamostat, granisetron, oral clonidine, cold saline solution, ketorolac, thiopental, magnesium sulfate, ephedrine, or the topical application of nitroglycerine, EMLA, or 60% lidocaine band [7–15].

Although the mechanism of the pain which occurs during propofol injection has not been fully clarified, there are known to be several factors which have an effect. These are the administration of the injection to veins in the dorsal area of the hand, the temperature of the propofol formulation, the rate of administration of the drug, aqueous phase propofol concentration, the buffering effect of the blood and administration

together with agents such as opioids and local anaesthetics [16].

Lornoxicam (aka chlorotenoxicam) is a non-steroid anti-inflammatory drug (NSAID) of the oxycam family. It is available in oral and parenteral forms. Unlike other known oxycams, elimination half life of lornoxicam is relatively short (circa four hours), which is advantageous with respect to tolerability [17].

Although the mechanism responsible for the pain associated with propofol injection is not fully known, it is, however, thought to involve the activation of the kinin cascade system and other pain mediators. Our hypothesis is that the anti-inflammatory properties of lornoxicam can reduce propofol injection pain. Consequently, we undertook the present study to evaluate the efficacy of lornoxicam in the prevention of propofol pain. To the best of our knowledge, there have been no prior studies in the literature addressing this topic. The aim of the present study was to investigate the role and effective dose of lornoxicam in preventing the pain associated with the intravenous injection of propofol.

## Material and Method

Approval for the study was granted by the Ethics Committee of Dicle University Medical Faculty. The study included a total of 120 patients, aged 18–65 years, of ASA I-II, who were to undergo elective

surgery. The patients had no contraindications for general anaesthesia and had no allergic reactions to the drugs to be used. Written informed consent was obtained from all the patients. Exclusion criteria were pregnancy, extensive heart and circulatory system impairment, respiratory tract disease, neurological diseases, liver and kidney function impairments, bleeding and clotting problems, a history of gastrointestinal ulcer or non-acceptance of the procedure.

Using a computer-generated randomisation program, the patients were allocated to one of four groups of 30 patients each. Immediately before anaesthesia induction, a syringe injector of 10 ml equivalent was prepared for each patient. The syringe injectors were prepared for Group I (control) with 10 ml isotonic 0.9% NaCl solution. For Groups II, III and IV, the same solution contained 2 mg, 4 mg and 8 mg of lornoxicam (Xefo, Abdi Ibrahim, Turkey) respectively. The assistant preparing the drugs wrote the group number on the outside of each syringe injector. Then the drug amount, colour and group number were covered with a plaster so as not to be visible and the syringe injector was given to another assistant in the operating theatre who was blinded to the study groups.

Routine monitoring was applied to all patients in the operating theatre with 3-channel electrocardiography (ECG), peripheral oxygen saturation (SpO<sub>2</sub>) and noninvasive arterial pressure monitoring (Nihon Kohden/Japan). No premedication was applied to the patients. A 20-gauge intravenous cannula was placed in the dorsal area of the hand. Also, an infusion of a Ringer Lactate solution (Na<sup>+</sup>: 130 mEq/L, K<sup>+</sup>: 4 mEq/L, Cl<sup>-</sup>: 109 mEq/L, lactate: 28 mEq/L) was started at the rate of 100 ml/hour.

To achieve a double-blind study, the syringe injectors were prepared and their contents were masked before an assistant took them to another in the operating theatre. For each patient, the syringe injector to be used was selected at random. To prevent serum circulation in the forearm, a tourniquet was applied for 2 minutes. A 2 mg/kg dose of propofol was calculated for each patient for anaesthesia induction in all groups. The drug (10 mg/ml ampoule) was supplied by Fresenius company (Bursa/Ankara, Turkey). In the operating room, first 25% of the calculated dose was injected over 10 seconds. Pain was evaluated by a different anaesthetist within the following 20 seconds, then the remainder of the propofol dose was given, and induction of anaesthesia continued.

Pain was evaluated by asking the patient to score the pain felt according to the following scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, as shown in Table 1. After completion of the IV anaesthesia agent injection, 0.15 mg/kg vecuronium (Norcuron 2 mg/ml, Organon, Turkey) was used for oral intubation. Following intubation, 1 mcg/kg fentanyl (50 mcg/ml Fentanyl Citrate, Abbott, Turkey) was added. The surgical procedure was then started. Throughout the operation, patients were monitored with ECG, systemic blood pressure and SpO<sub>2</sub> values. Systemic blood pressure was measured with the non-invasive oscillometric method.

After completing the pain evaluation, the plaster covering the details on the syringe injector was removed by another assistant and the group number written on the syringe injector was recorded on the prepared form, together with the patient demographic data and pain scores. All patients were followed up for 24 hours for pain, oedema, inflammation and allergic reactions which might have developed in the injection site.

Power analysis in the current study was calculated on the assumptions that the incidence of pain associated with the propofol injection without pre-medication would be 65%, and with premedication 35% [5]. Based on these assumptions, a total of 48 subjects was necessary to determine a significant difference at 80% power per group (one-way,  $\alpha = 0.05$ ). The current study was planned with a total of 120 subjects – 30 cases per group. Continuous and categorical data were analysed using the one-way ANOVA and Chi-square tests. Statistical analysis of the data was made using SPSS for Windows v. 13.0 software (Statistical Package for Social Sciences SPSS Inc. Chicago, IL, USA). Differences between the groups in the severity of pain were evaluated using the Chi-square test. The Mann Whitney U-test and the Kruskal Wallis tests were applied. A value of  $p < 0.05$  was accepted as statistically significant.

## Results

The study included a total of 120 patients randomly allocated to four equal groups of 30. The demographic data such as age, sex, body weight and additional features were evaluated in each group. No statistically significant difference was determined between the groups in respect of demographic data. Due to the randomisation system, the groups were not homogenous and a statistically significant difference was observed between the groups in respect of

**Table 1.** Verbal pain scale.

No pain	Mild pain	Moderate pain	Severe pain
(The patient stated that they felt pain or burning, without a behavioural response and without grimacing)	(The patient stated pain or burning with a grimace; the pain was reported without asking)	(The patient withdrew their arm with pain and crying)	
0	1	2	3

the number of males and females ( $p < 0.05$ ). There were more females in Groups I and II, while in Groups III and IV the numbers of males and females were comparable (Table 2).

To determine an effective dose of lornoxicam, doses of 2 mg, 4 mg, and 8 mg were compared with the control group. Pain associated with propofol injection was seen at 93.3% in the control group and the overall incidence of pain was 83.3% (Table 3). No difference was observed in the incidence of pain between Group I (control) and Group II (2 mg). In Group III (4 mg), a significant reduction in pain was observed ( $p = 0.015$ ). While the incidence of pain in Group II (2 mg) was not significantly different from that observed in the control group (Table 3), none of the patients in Group II experienced severe pain (Tables 4).

When the severity of pain during propofol injection was evaluated, a statistically significant reduction in the severity of pain was seen between Groups I and II ( $p = 0.0002$ ), between Groups I and III ( $p = 0.0001$ ), between Groups I and IV ( $p = 0.00001$ ) and between Groups II and III ( $p = 0.026$ ). No statistically significant difference was determined in the severity of pain between Groups III and IV ( $p = 0.401$ ) (Table 4).

statistically significant difference in the severity of pain was observed in all the lornoxicam groups compared with the control group. Pretreatment with 4 mg of lornoxicam was as effective in the reduction of propofol pain as the pretreatment with 8 mg. While pretreatment with 2 mg lornoxicam did not affect the incidence of propofol pain, it significantly reduced its severity compared to the control group. The use of 4 mg and 8 mg lornoxicam was found to be effective in the reduction of both the incidence and severity of the pain associated with propofol injection. When the severity of pain during propofol injection was evaluated according to sex, no statistically significant differences were found between the groups (Table 4).

Table 2. Demographic data.

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	Group IV (n = 30)	p value
Age (mean $\pm$ 1SD <sup>1</sup> ), years	29.8 $\pm$ 9.6	29.6 $\pm$ 8.5	35.2 $\pm$ 11.0	30.2 $\pm$ 8.6	0.075
Sex, n					
Male	9 (30%)	9 (30%)	15 (50%)	14 (46%)	0.043
Female	21 (70%)	21 (70%)	15 (50%)	16 (54%)	
Body weight (mean $\pm$ 1SD), kg	65.5 $\pm$ 9.2	63.8 $\pm$ 11.3	70.8 $\pm$ 11.9	67.3 $\pm$ 11.1	0.087
ASA, n <sup>2</sup>					
I	13 (43%)	18 (60%)	8 (27%)	14 (46%)	
II	17 (57%)	12 (40%)	22 (73%)	16 (54%)	
Additional features, n					
DM <sup>3</sup>	2	0	4	1	
HT <sup>4</sup>	3	3	1	2	
Smoking	19	16	21	20	

Results given as mean  $\pm$  standard deviation (SD). In the comparison of age, sex, bodyweight, the one-way ANOVA test was used.

<sup>1</sup>SD: Standard deviation; <sup>2</sup>ASA: American Society of Anesthesiologists; <sup>3</sup>DM: Diabetes Mellitus; <sup>4</sup>HT: Hypertension

Table 3. Pain incidence during propofol injection.

	Pain (-)	Pain (+)
Group I (n = 30)	2 (6.7%)	28 (93.3%)
Group II (n = 30)	2 (6.7%)	28 (93.3%)
Group III (n = 30)	10 (33.3%)	20 (66.7%)
Group IV (n = 30)	6 (20%)	24 (80%)
Total (n = 120)	20 (16.7%)	100 (83.3%)

Table 4. Distribution of the severity of pain during propofol injection and according to sex.

	No pain	Mild pain	Moderate pain	Severe pain
Groups				
Group I (n = 30)	2 (6.7%)	7 (23.3%)	7 (23.3%)	14 (46.6%)
Group II (n = 30)	2 (6.7%)	18 (60%)	10 (33.3%)	None
Group III (n = 30)	10 (33.3%)	15 (50%)	4 (13.3%)	1 (3.3%)
Group IV (n = 30)	6 (20%)	20 (66.7%)	3 (10.0%)	1 (3.3%)
Sex				
Female (n = 73)	10 (13.7%)	34 (46.6%)	19 (26.0%)	10 (13.7%)
Male (n = 47)	10 (21.3%)	26 (55.3%)	5 (10.6%)	6 (12.8%)
Total (n = 120)	20 (16.7%)	60 (50%)	24 (20%)	16 (13.3%)

## Discussion

In this study which investigated the efficacy of lornoxicam in the prevention of pain which occurs as a result of propofol injection, it was concluded that lornoxicam reduced the severity of pain in all the groups. The mechanism of propofol injection pain involves the release of kinins as a result of direct irritation of vascular endothelium (especially tunica media and intima) by propofol. Propofol frees bradykinin by activating the kinin-kallikrein system, and thereby causing venous dilation and hyperpermeability. This creates pain by creating greater contact of propofol with free nerve ends. Slow administration of the injection causes greater pain by removing the interaction of the propofol active component with the endothelium [18]. The effect of lornoxicam is based on the inhibition of the synthesis of

prostaglandins (PGs), which are mediators of inflammation [19]. The selection of lornoxicam in the present study was based on the PG inhibition potential of an NSAID resulting in the inhibition of the kinin cascade.

Various drugs and methods have been used to reduce the incidence or the severity of propofol injection pain. The most effective method has been reported to be the injection of 0.5 mg/kg lidocaine, which causes venous occlusion, before the administration of propofol [19]. In a study by Liley et al., the addition of lidocaine to the propofol emulsion was shown to reduce pain incidence by destabilising the emulsion [20]. In another study which compared lidocaine, saline and metoprolol in the prevention of propofol pain, metoprolol was found to be as effective as lidocaine [16].

Niazi et al. [21] reported that the total injection given at a rate of 10–20 seconds could reduce or delay pain. In the current study, the propofol injection was calculated to be given at the rate of 10 seconds. The slow IV injection was set to give 25% of the total dose in 10 seconds and the patient was questioned about the incidence of pain 20 seconds after the injection. The purpose of adjusting the rate in this way was to be able to evaluate the pain effect of delayed propofol effect. This is because the indirect effect of kinin activation caused by the direct irritant effect of propofol is thought to be responsible for injection pain [22].

In a study by Canbay et al. [23] using acetaminophen, which is an anilide group analgesic, the pain incidence was seen to be 64% in the control group, 22% in the acetaminophen group and 8% in the lidocaine group. It was concluded that pretreatment with 50 mg IV acetaminophen was determined to be effective in reducing propofol injection pain. NSAIDs have also been used previously as pretreatment for propofol injection pain. Fujii et al. [24] determined pain incidence as 90% in a control group and reported that pretreatment with 50 mg and 75 mg flurbiprofen axetil was effective in the reduction of severity and prevention of propofol injection pain.

In our study, lornoxicam was used as NSAID and comparison with the control group was made of doses of 2 mg, 4 mg and 8 mg. Canbay et al. [23] compared a single dose of acetaminophen with lidocaine and a control group. In the present study, we observed a 93% incidence of pain in the control group. Our results indicate that pretreatment with 4 mg or 8 mg lornoxicam is effective in reducing both the incidence and the severity of the pain associated with propofol injection.

To the best of our knowledge, there is no study in the literature which has investigated lornoxicam pretreatment for reducing propofol pain. There is a need for further studies to compare this efficacy with other pretreatments, especially lidocaine. In the present

study we found no statistically significant difference between males and females with respect to incidence or severity of propofol pain. However, because gender distribution in our study was uneven, no definitive conclusions can be made with respect to incidence and severity of pain in males vs females.

## Conclusion

Pretreatment with 4 mg and 8 mg of lornoxicam is effective in reducing both the incidence and the severity of the pain associated with propofol injection. Maximum effect is obtained with dose of 4 mg.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## Notes on contributor

Both authors contributed to the design of the study, collection of data and writing of the article. Both authors have read and approved the final version of the article.

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