

# Dexketoprofen versus Tenoxicam in Acute Severe Pain Due to Primary Dysmenorrhea

Deniz Aka Satar<sup>1</sup>, Salim Satar<sup>2</sup>, Muge Gulen<sup>2</sup>, Selen Acehan<sup>2</sup>, Nefise Tanridan Okcu<sup>3</sup> and Gonca Koksaldi Sahin<sup>2</sup>

<sup>1</sup>Assisted Reproduction Unit, Andrology Laboratory, Health Sciences University, Adana City Training and Research Hospital, Adana, Turkiye

<sup>2</sup>Emergency Medicine Clinic, Health Sciences University, Adana City Training and Research Hospital, Adana, Turkiye

<sup>3</sup>Department of Obstetrics and Gynaecology, Health Sciences University, Adana City Training and Research Hospital, Adana, Turkiye

## ABSTRACT

**Objective:** To evaluate the analgaesic efficacy of tenoxicam and dexketoprofen in patients admitted to the Emergency Medicine (EM) Clinic with severe acute pain due to primary dysmenorrhea (PD).

**Study Design:** Randomised-controlled trial.

**Place and Duration of the Study:** Emergency Medicine Clinic, Health Sciences University, Adana City Training and Research Hospital, Adana, Turkiye, from January to December 2022.

**Methodology:** Patients presenting with PD, were divided into two groups of 60 each, administered 50 mg dexketoprofen and 20 mg tenoxicam intravenously. Visual analogue scale (VAS) scores were recorded at the 15<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, and 120<sup>th</sup> minutes. VAS scores and  $\Delta$ VAS scores were compared with the effectiveness of drugs, the need for rescue drugs and its side-effects.

**Results:** Intravenous (IV) dexketoprofen was administered to 60 of the patients and IV tenoxicam was administered to another 60. At the time of admission, mean VAS scores of the patients were  $8.8 \pm 0.9$  for the dexketoprofen group and  $8.6 \pm 0.8$  for the tenoxicam group. The VAS scores of the dexketoprofen group were found to be statistically significantly lower after 30 minutes with lower need for rescue analgaesics.  $\Delta$ VAS scores of the dexketoprofen group were statistically significantly higher from the 30<sup>th</sup> minute.

**Conclusion:** According to the VAS scoring, IV dexketoprofen was a more effective drug than IV tenoxicam in patients who were admitted to the EM clinic with severe pain due to PD.

**Key Words:** Dexketoprofen, Primary dysmenorrhea, VAS score.

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## INTRODUCTION

Primary dysmenorrhea (PD) is a clinical diagnosis that starts just before or with menstrual bleeding and gradually decreases within 12-72 hours, and recurs usually in the form of cramps in the pelvic midline and in the absence of any other pathology that could explain the pain. Symptoms are similar to any other menstrual cycle and may recur. The prevalence of PD ranges from 50 to 95 percent.<sup>1</sup> When dysmenorrhea is severe, it causes impaired quality of life, absenteeism from school, decreased productivity related to work and other responsibilities, and reduced social activities.<sup>2</sup>

PD is associated with the ovulatory menstrual cycle. Prostaglandins mediate this inflammatory response, which causes uterine hypercontractility, decreased blood flow, and hypersensitisation of pain fibres, and cramping abdominal pain.<sup>3</sup>

Studies have shown that women with dysmenorrhea have high prostaglandin levels. However, high prostaglandin levels in the endometrium of women with PD were found within the normal limits in plasma.<sup>4</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) act by blocking prostaglandin production by inhibiting the use of cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins. They are generally first-line drugs for acute pain due to PD.<sup>4</sup>

Tenoxicam is an NSAID from the Oxicam class. It achieves its analgaesic and antipyretic effects through non-selective inhibition of COX 1 and 2. Its systemic clearance is low and has a low volume distribution. It binds to protein with 99% and is completely absorbed after the oral administration. Its half-life is nearly three days. It is completely metabolised to inactive metabolites that are excreted in the urine and faeces.<sup>5</sup>

Dexketoprofen is the propionic acid derivative - (S+) enantiomer of ketoprofen. It is an NSAID that has analgaesic and antipyretic properties and achieves these effects by inhibition of COX 1 and 2. Its effect begins approximately 30 minutes after the oral administration and lasts for approximately 4-6 hours. It is mainly excreted by the kidneys and does not accumulate in the body.<sup>6</sup>

Correspondence to: Dr. Deniz Aka Satar, Assisted Reproduction Unit, Andrology Laboratory, Health Sciences University, Adana City Training and Research Hospital, Adana, Turkiye

E-mail: denizakasatar@yahoo.com

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The aim of this study was to evaluate the analgaesic efficacy of tenoxicam and dexketoprofen in patients who presented to the EM clinic with severe acute pain due to PD.

## METHODOLOGY

This study was a double-blind, randomised, controlled trial conducted prospectively. It was started after the approval of the Ethics Committee (Approval no. 1715, dated 30 December 2021). The study was conducted between January and December 2022 at the Emergency Medicine Clinic, University of Health Sciences, Adana City Training and Research Hospital, Turkiye.

Patients were randomised by pre-determining the inclusion and exclusion criteria from the study. Patients with a diagnosis of PD and who had regular menstruation, aged 18-40 years, agreed to participate in the study, and patients with VAS score >5 were included in the study. Patients with peritoneal irritation symptoms and suspected acute abdomen on the physical examination, secondary dysmenorrhea, with any history of urticarial or allergy reaction to NSAIDs, upper gastrointestinal bleeding history and/or an active peptic ulcer history, those on contraception methods, patients with kidney and liver failure, patients with chronic upper gastrointestinal system disease, patients with allergic rhinitis or nasal polyps history, patients who used analgaesics for pain in the last six hours before admission to the EM clinic were excluded from the study.

One hundred and forty-four patients presented to the EM clinic with abdominal pain due to dysmenorrhea during the study period. One hundred and twenty patients were included after exclusion. Of the patients who admitted with a preliminary diagnosis of dysmenorrhea, 5 had peritoneal irritation findings, 5 patients had a history of contraception (oral contraceptive) use, 1 patient had a history of ulcerative colitis, 2 patients had a history of allergic rhinitis, and 2 patients had a history of active peptic ulcer. Five patients had taken NSAIDs in the last six hours before presenting to the EM clinic. Four patients did not consent to be included in the study.

A randomisation schedule was designed on SPSS software programme by a statistics expert who was blinded to the study. Later, once a blinded physician obtained the informed consent forms, he assigned a number for each eligible patient in a sealed envelope. The study numbers as well as the information on which patients were paired with a drug were known only to this blinded physician until the study was over. The physicians and patients did not know which treatment was applied. Randomisation order was made according to the order of admission to the emergency department. The study numbers and drug information were kept in opaque envelopes. After opening these envelopes in order, one of the ED nurses prepared the drug written in the envelope as described below.

The patients were divided into two groups. Sixty patients were administered IV dexketoprofen (Group 1), and 60 patients IV tenoxicam (Group 2). Group 1 was administered 50 mg of dexketoprofen (Ketavel, Deva, Turkiye) and Group 2 was given 20 mg of

tenoxicam (Tilcotil, Deva, Turkiye). The drugs were administered via IV infusion in 100 mL of saline in 20 minutes. In order to eliminate the colour differences, solutions were covered with an opaque white colour. The drugs were prepared by one nurse only. Another nurse administered the drugs numbered according to the randomisation. The patients were observed for 120 minutes after infusion was completed. Patients with VAS score <5 were discharged after this period. They were all recommended to visit an obstetrics outpatient clinic. A dose of 1000 mg of paracetamol (Paracerol 10 mg/ml, Polifarma, Turkiye) was given IV as an additional drug to those with a VAS score >5 at the 60<sup>th</sup> minute of the observation period. Patients who were administered additional drug were observed until their VAS score fell <5 at the observation room.

To evaluate the level of pain, a VAS score (0-10 cm) was used. Before and during the treatment, all VAS scores were recorded in a chart. The VAS scores were not shown or told to the patients. The measurements were done and recorded at the 0<sup>th</sup> minute immediately after the drug was discontinued, and then at the 15<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup>, and 120<sup>th</sup> minutes. All of the VAS score markings were done by the patients before and during the procedure by the patients themselves. The patients did this regardless of the previous marking. All of the VAS score charts were loaded at any step of the study. Pain measurements were made and recorded at the 0<sup>th</sup> minute after the drug was discontinued, and then at the 15<sup>th</sup>, 30<sup>th</sup>, 60<sup>th</sup> and 120<sup>th</sup> minutes.  $\Delta$ VAS ( $\Delta$ VAS15,  $\Delta$ VAS30,  $\Delta$ VAS60,  $\Delta$ VAS120) was evaluated to reduce the bias of individual variation in VAS score.

$$\Delta$$
VAS15 = (VAS0-VAS15)/VAS0     $\Delta$ VAS30 = (VAS0-VAS30)/VAS0  
 $\Delta$ VAS60 = (VAS0-VAS60)/VAS0     $\Delta$ VAS120 = (VAS0-VAS120)/VAS0

The sample size was estimated with G\*Power for MacOS X (version 3.1.9.2; *Universität Dusseldorf*, Germany). Accordingly, with a Type-1 error of 5%, a Type-2 error of 5% (power 95%), and a two-sided analysis, the sample size was determined as 96 patients. Considering a possible protocol bias, adding 10% of patients to each arm was planned; hence, 106 were determined as the minimum number of patients to be included. All of the demographic characteristics and the patient numbers were recorded. Adverse effects (epigastric pain, nausea, vomiting) occurring during the drug administration and follow-up period were recorded. Symptoms such as nausea and vomiting due to dysmenorrhea before the treatment were not considered as side-effects. Any adverse effects due to the drugs were treated asymptotically.

The primary outcome of this study was to reveal the analgaesic efficacy between tenoxicam and dexketoprofen. The secondary outcome was to reveal the need for rescue drugs and the side-effects of these drugs.

SPSS 25 (SPSS Inc, Chicago, Illinois, USA) package programme was used in the statistical evaluation of the data. The continuous data were summarised as standard deviation and mean, while the categorical data were summarised as percentages and numbers. The categorical data were compared with the Chi-square test. A normality test (Kolmogorov Smirnov test) was

used to determine if the sample data had been drawn from a normally distributed population. The Mann-Whitney U test was used when the variables were not normally distributed. When the variables were normally distributed, the Student's t-test was used. Ap-value of <0.05 was considered statistically significant.

## RESULTS

One hundred and twenty patients were included in this study. Patients' pulse rate, mean arterial pressure, body mass index (BMI), menarche age, menstrual flow duration, duration of pain, endometrial thickness, menstrual cycle duration, and the mean age were not statistically significant when compared between the groups (Table I). Rescue analgaesic (1000 mg paracetamol IV) was needed in two patients (3.3%) in Group 1 and 8 patients (13.3%) in Group 2. Need for rescue analgaesics was statistically significant ( $p = 0.048$ , Table I).

While 7 patients who were administered dexketoprofen complained of nausea, vomiting, and epigastric pain, 9 patients who received IV tenoxicam complained of vomiting, nausea, and epigastric pain. It was not statistically significant ( $p = 0.872$ , Table II).

On admission, the mean VAS scores of the patients were  $8.8 \pm 0.9$  for Group 1 and  $8.6 \pm 0.8$  for Group 2 (Table III). It was not statistically significant ( $p = 0.406$ ). The VAS scores were statistically significantly lower ( $p = 0.036$ ) and the  $\Delta$ VAS scores were statistically significantly higher in Group 1 ( $p < 0.001$ ) firstly from 30<sup>th</sup> minute of drug administration (Table III).

The decrease in the mean VAS score from the 30<sup>th</sup> minute was significantly higher in Group 1 (dexketoprofen) than in Group 2 (tenoxicam, Figure 1).

**Table I: Baseline and demographic characteristic of patients.**

Variables	Group 1 (Dexketoprofen) (n=60)	Group 2 (Tenoxicam) (n=60)	p-value
Age (years)	27.2 $\pm$ 4.8	26.6 $\pm$ 5.1	0.523*
Pulse (beat/min)	83.5 $\pm$ 6.3	83.1 $\pm$ 6.1	0.736*
Mean arterial pressure (mmHg)	91.3 $\pm$ 4.8	89.7 $\pm$ 5.2	0.086*
BMI (kg/m <sup>2</sup> )	21.7 $\pm$ 1.1	21.4 $\pm$ 1.2	0.084*
Menarche age (years)	13.1 $\pm$ 1.2	13.2 $\pm$ 1.3	0.945*
Menstrual cycle duration (days)	27.6 $\pm$ 1.8	27.6 $\pm$ 1.9	0.885*
Menstrual flow duration (days)	5.5 $\pm$ 0.8	5.6 $\pm$ 0.9	0.362*
Duration of pain (days)	2.1 $\pm$ 0.7	2.1 $\pm$ 0.8	0.800*
Endometrial thickness	10.1 $\pm$ 1.6	10.1 $\pm$ 1.5	0.953*
Rescue drug needed n (%)	2 (3.3)	8 (13.3)	0.048**

\* Student's t test, \*\* Chi-square test.

**Table II: Side-effects of dexketoprofen and tenoxicam.**

Side-effects	Group 1 (Dexketoprofen) (n=60)	Group 2 (Tenoxicam) (n=60)	p-value
Nil	53 (88.3)	51 (85)	0.872*
Nausea	3 (5)	3 (5)	
Emesis	2 (3.3)	4 (6.7)	
Epigastric pain	2 (3.3)	2 (3.3)	

\* Chi-square test.

**Table III: Comparison of delta values and mean of VAS scores.**

	Group 1 (Dexketoprofen) (n=60)	Group 2 (Tenoxicam) (n=60)	p-value*
VAS0	8.8 $\pm$ 0.9	8.6 $\pm$ 0.8	0.406
VAS15	8 $\pm$ 1	8 $\pm$ 0.8	0.758
VAS30	5.9 $\pm$ 0.6	6.2 $\pm$ 0.7	0.036
VAS60	4 $\pm$ 0.8	4.5 $\pm$ 0.9	0.001
VAS120	2.1 $\pm$ 0.5	2.4 $\pm$ 0.8	0.004
$\Delta$ VAS15	0.09 $\pm$ 0.05	0.08 $\pm$ 0.06	0.248
$\Delta$ VAS30	0.32 $\pm$ 0.05	0.28 $\pm$ 0.06	<0.001
$\Delta$ VAS60	0.55 $\pm$ 0.08	0.48 $\pm$ 0.07	<0.001
$\Delta$ VAS120	0.76 $\pm$ 0.05	0.72 $\pm$ 0.08	<0.001

VAS: Visual Analogue Scale

VAS0: On admission

VAS15: 15 minutes after drug admission

VAS30: 30 minutes after drug admission

VAS60: 60 minutes after drug admission

VAS120: 120 minutes after drug admission

$\Delta$ VAS15 = (VAS0-VAS15)/VAS0

$\Delta$ VAS30 = (VAS0-VAS30)/VAS0

$\Delta$ VAS60 = (VAS0-VAS60)/VAS0

$\Delta$ VAS120 = (VAS0-VAS120)/VAS0

\* Student's t-test.

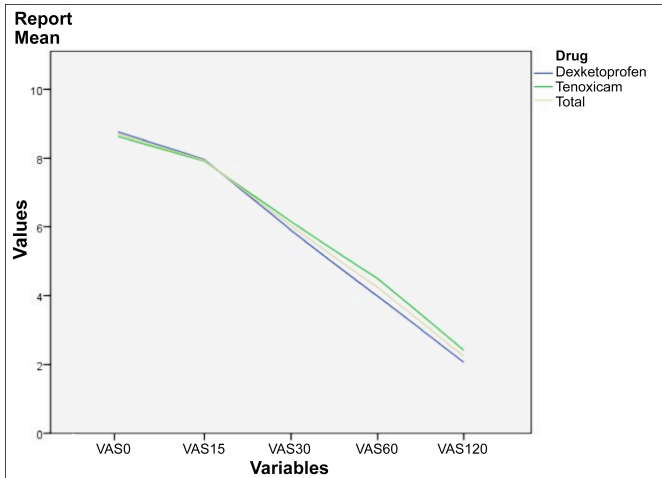


Figure 1: Mean VAS scores at each time.

## DISCUSSION

High levels of  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  were detected in the menstrual fluid, and endometrium of adolescents with dysmenorrhea are the most acknowledged theory to explain the aetiology of this syndrome.<sup>7</sup> A high  $\text{PGF}_{2\alpha}/\text{PGE}_2$  ratio occurs in the menstrual blood of patients with PD.<sup>4</sup>  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  cause myometrial contraction and vasoconstriction leading to ischaemia and pain. They can also cause hypersensitivity of target neurons to physical and chemical stimuli. Intrauterine administration of  $\text{PGF}_{2\alpha}$  has been shown to cause uterine contractility and dysmenorrhea-like pain.<sup>8</sup>

NSAIDs are classified as prostaglandin synthetase (PG) inhibitors and are among the most commonly prescribed drug groups globally.<sup>6</sup> Due to the prostaglandin-based aetiology of PD, the most common pharmacological treatment prescribed for dysmenorrhea is NSAIDs.<sup>4</sup> Various formulations of NSAIDs have comparable efficacy for dysmenorrhea and pain relief is successfully achieved in 64-100% of women.<sup>7</sup> However, unfortunately, 15% of women with dysmenorrhea do not respond to or do not tolerate PG inhibitors.<sup>9</sup>

In this study, the analgaesic efficiency of dexketoprofen was statistically significantly higher after the 30<sup>th</sup> minute from administration as compared to tenoxicam. Dexketoprofen is a non-selective NSAID of the aryl propionic acid group containing the active S-enantiomer of racemic ketoprofen. It is an NSAID with a relatively short half-life and rapid onset of action, and hence it is very effective in the treatment of inflammatory pain.<sup>10</sup>

It has been reported to be effective in the symptomatic treatment of mild-to-severe pain.<sup>11-13</sup> In another article evaluating randomised controlled studies, systematic reviews, and meta-analyses, it was stated that dexketoprofen is fast and effective in acute pain situations and has an opioid-sparing effect.<sup>14</sup> In a randomised-controlled study involving patients presenting with renal colic, it was found to be more effective than fentanyl, an opioid, in reducing the severity of pain.<sup>15</sup> In

another randomised-controlled study, the effect of dexketoprofen was compared with paracetamol in patients suffering from PD. It was stated that dexketoprofen and paracetamol were effective in reducing pain in patients with PD. Although the authors achieved better VAS scores after dexketoprofen administration but this was not statistically significant.<sup>16</sup> In a randomised-controlled study conducted in patients presenting with PD, dexketoprofen was compared with ketoprofen, and no difference was found between the two drugs, but it was reported that dexketoprofen affected pain more rapidly.<sup>17</sup>

Tenoxicam is a long-acting NSAID in the oxicam group that is widely used in the treatment of rheumatoid arthritis, osteoarthritis, acute gout, and other extra-articular diseases. There are studies in the literature showing the analgaesic efficacy of tenoxicam in gynaecological pathologies, but its efficacy in dysmenorrhea has not been studied yet.<sup>1</sup> Uterine cramps after postpartum cesarean section are dysmenorrhea-like pains. It has been shown that tenoxicam used in the preoperative period in patients who will be operated due to cesarean section can reduce postoperative opioid use.<sup>18</sup>

It had been suggested that 20 mg IV tenoxicam may be effective in patients who undergo cesarean section in the preoperative period. However, it was used with topical pain relievers in this study.<sup>19</sup>

The administration of tenoxicam after postpartum cesarean section had been shown to be effective in relieving pain associated with uterine cramps. In this study, 40 mg IV tenoxicam was used.<sup>20</sup> In a similar study using 20 mg of tenoxicam, it was shown that the pain associated with cramps was reduced by 33%.<sup>21</sup> In this study, 20 mg IV tenoxicam was used.

Although tenoxicam was effective in relieving pain, its analgaesic effectiveness was less than that of dexketoprofen. Tenoxicam, which is in the Oxicam group, is a drug with hydrophilic character because a thienothiazine system of the benzothiazine ring had been added. Tenoxicam, therefore, showed lower penetration into tissues that required more lipophilic properties.<sup>22</sup> Uterus is a tissue where lipophilic agents penetrate better.<sup>23</sup> Tenoxicam is half as active piroxicam at steady state plasma concentrations, and it has moderate inhibitory activity on PG synthesis and release.<sup>22</sup> The lower analgaesic efficacy of tenoxicam as compared to dexketoprofen and the need for more rescue analgaesics in this study may be related to these reasons.

Various NSAIDs had comparable safety and efficacy in the management of pain associated with PD, and it may be said that one formulation is not superior to the other.<sup>7</sup> The time of administration of the NSAID may determine its effectiveness.<sup>24</sup> Delay in taking NSAIDs with or before symptoms may suppress prostaglandin synthesis gradually or incompletely.<sup>25</sup> In one of the studies, including systematic analysis of 80 randomised-controlled studies and 5820 patients, it was stated that NSAIDs

were more than twice as effective as paracetamol and 4.5 times more effective than a placebo for pain relief, and they were not superior to each other in pain relief. The quality of the evidence for most comparisons was reported as low due to under-reporting of the study methods.<sup>26</sup>

The gastrointestinal side-effects were observed in the study, but no statistically significant difference was found between the two groups.

There were some limitations of this study. Since the study was a superiority trial, and it was not possible to conclude that the two drugs are equal. There was no data whether the patients attended another healthcare centre after being discharged from the authors' emergency service.

### CONCLUSION

IV dexketoprofen was a more effective drug than IV tenoxicam in patients who were admitted to the EM clinic with severe pain due to PD. In addition, neither dexketoprofen nor tenoxicam had a high adverse effect profile.

### ETHICAL APPROVAL:

All procedures performed in this study involving the human participants were in accordance to the ethical standards of institutional research committee. For this study, an approval was obtained from the Ethics Committee with the decision dated 30.12.2021 and numbered 96/1715. The study was carried out according to the 1964 Declaration of Helsinki and Good Clinical Practice Guidelines.

### PATIENTS' CONSENT:

Informed consent was obtained from all patients.

### COMPETING INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

DAS: Principal investigator, conception and design investigations of work, and write-up.

DAS, SA, MG, SA: Supervisor, critical analysis, and data analysis and interpretation.

MG, SA, NTO, GKS: Data analysis, SPSS analysis, and proof-reading.

All authors approved the final version of the manuscript to be published.

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