ORİJİNAL MAKALE / ORIGINAL ARTICLE

Balıkesir Sağlık Bilimleri Dergisi / BAUN Sağ Bil Derg
Balıkesir Health Sciences Journal / BAUN Health Sci J
ISSN: 2146-9601- e ISSN: 2147-2238
Doi: https://doi.org/10.53424/balikesirsbd.1740346

Administration of Preoperative Meloxicam and Firocoxib on Postoperative Analgesia and Inflammatory Markers in Dogs Undergoing Ovariohysterectomy

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Geliş Tarihi / Received: *11.07.2025*, ***Kabul Tarihi / Accepted:*** *02.09.2025*

ABSTRACT

Objective: The objective of this study was to evaluate the postoperative analgesic and anti-inflammatory effects of meloxicam and firocoxib in dogs undergoing ovariohysterectomy (OHE). **Materials and Methods:** Thirty healthy female dogs were randomly assigned to three groups: 0.2 mg/kg subcutaneous meloxicam, 5 mg/kg oral firocoxib, or no preoperative non-steroidal antiinflammatory drug (control). The Glasgow Composite Measure Pain Scale – Short Form (CMPS-SF), rectal temperature, and heart rate were recorded preoperatively and at 1, 2, 3, 4, and 24 hours postoperatively. Blood samples were collected at each time point to assess cortisol levels and calculate the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). **Results:** CMPS-SF scores significantly increased at 1 hour postoperatively in all groups ($p<0.05$), with the control group showing the highest pain scores. Scores remained elevated at 4 hours. Cortisol levels increased approximately 4-fold at 1 hour, 5-fold at 2 hours, and 4-fold at 4 hours postoperatively, returning to baseline by 24 hours ($p<0.05$). Rectal temperature and heart rate exhibited a gradual increase toward preoperative values following an initial decrease in the early postoperative period. Rescue analgesia was required in three dogs—two in the firocoxib group and one in the control group. At 24 hours, NLR and SII were significantly higher in the control group compared to the treatment groups ($p<0.05$). However, no significant differences were observed between groups in CMPS-SF scores or cortisol levels during the first 4 postoperative hours. **Conclusion:** Both meloxicam and firocoxib were effective in reducing systemic inflammatory responses at 24 hours post-OHE. Although there were no significant differences in early postoperative pain scores or cortisol levels, meloxicam group required fewer instances of rescue analgesia compared to the firocoxib group.

Keywords: Dog, Firocoxib, Meloxicam, NLR, Pain.

Ovariohisterektomi Öncesinde Köpeklerde Preoperatif Meloksikam ve Firokoksibin Uygulamasının Postoperatif Analjezi ve İnflamatuvar Belirteçler Üzerine Etkisi

ÖZ

Amaç: Bu çalışmanın amacı, ovariohisterektomi (OHE) uygulanan köpeklerde meloksikam ve firokoksibin postoperatif analjezik ve anti-inflamatuvar etkilerini değerlendirmektir. **Materyal ve Yöntem**: Otuz sağlıklı dişi köpek rastgele üç gruba ayrıldı: 0.2 mg/kg subkutan meloksikam, 5 mg/kg oral firokoksib veya preoperatif nonsteroid anti-inflamatuar ilaç uygulanmayan kontrol grubu. Glasgow Bileşik Ağrı Ölçeği – Kısa Formu (CMPS-SF), rektal sıcaklık ve kalp atım hızı operasyon öncesinde ve postoperatif 1., 2., 3., 4. ve 24. saatlerde kaydedildi. Aynı zaman dilimlerinde kan örnekleri alınarak kortizol düzeyleri ile nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve sistemik immün-inflamasyon indeksi (SII) değerlendirildi. **Bulgular:** CMPS-SF skorları postoperatif 1. saatte tüm gruplarda anlamlı şekilde arttı ($p<0.05$) ve kontrol grubunda en yüksek düzeyde gözlendi. Skorlar 4. saatte de yüksek seyretti. Kortizol düzeyleri postoperatif 1. saatte yaklaşık 4 kat, 2. saatte 5 kat, 4. saatte ise tekrar 4 kat arttı ve 24. saatte bazal düzeye döndü ($p<0.05$). Rektal sıcaklık ve kalp atım hızı, operasyon sonrası erken dönemdeki başlangıç düşüşünü takiben preoperatif değerlere doğru kademeli bir artış gösterdi ($p<0.05$). Kurtarma analjezisi üç köpeğe uygulandı: iki köpek firokoksib grubunda, bir köpek ise kontrol grubundaydı. 24. saatte NLR ve SII değerleri kontrol grubunda tedavi gruplarına göre anlamlı olarak daha yüksekti ($p<0.05$). Ancak, postoperatif ilk 4 saat boyunca gruplar arasında CMPS-SF skoru ve kortizol düzeyleri açısından anlamlı fark gözlenmedi. **Sonuç:** Meloksikam ve firokoksib, OHE sonrası 24. saatte sistemik inflamatuvar yanıtı azaltmada etkili bulunmuştur. Erken postoperatif dönemde ağrı skorları ve kortizol düzeyleri bakımından gruplar arasında anlamlı fark olmamasına rağmen, meloksikam grubunda, firokoksib grubuna kıyasla daha az ek analjezi uygulamasına ihtiyaç duyulmuştur.

Anahtar Kelimeler: Ağrı, Firokoksib, Köpek, Meloksikam, NLR.

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Bu makaleye atıf yapmak için / Cite this article: Sahin, OA., Ozturk, B., Ayalp-Erkan, A. & Guner, B. (2025). Preoperative meloxicam and firocoxib on postoperative analgesia and ınflammatory markers in dogs undergoing ovariohysterectomy. BAUN Health Sci J, 14(3), 772-780. https://doi.org/10.53424/balikesirsbd.1740346

INTRODUCTION

Ovariohysterectomy (OHE) is among the most frequently performed elective surgical procedures in small animal veterinary practice, primarily for reproductive management and disease prevention (Caulkett et al., 2003; Hu et al., 2017). Despite its routine nature, OHE is associated with moderate to severe postoperative pain and inflammation, which, if inadequately managed, may compromise the recovery process. Effective control of postoperative pain and inflammation through appropriate analgesic strategies not only enhances patient comfort and promotes physiological healing but also plays a crucial role in preventing the transition to chronic pain states (Tsai et al., 2013; Karakaya Bilen et al., 2025).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed for managing postoperative pain due to their anti-inflammatory, analgesic, and antipyretic effects (Hernández-Avalos et al., 2020). They act primarily by inhibiting cyclooxygenase (COX) enzymes and subsequently reducing the production of prostaglandins involved in pain and inflammation. Among these, meloxicam and firocoxib represent commonly used NSAIDs in veterinary practice, each with different selectivity profiles for COX-2 inhibition (Gruet et al., 2013; McCann et al., 2004).

In addition to behavioral pain scoring systems, such as short-form Glasgow Composite Measure Pain Scale (CMPS-SF), various physiological and hematological parameters can provide objective insights into pain and inflammatory responses following surgical procedures. These include serum cortisol levels as a biomarker of stress and pain (Kim et al., 2012), heart rate and rectal temperature as indicators of autonomic nervous system activity (Tsai et al., 2013), and hematological indices like NLR, PLR, and SII, which are emerging as reliable markers of systemic inflammation and surgical stress (Espadas-González et al., 2023).

Therefore, the aim of this study was to investigate and compare the postoperative analgesic and anti-inflammatory effects of meloxicam and firocoxib in dogs undergoing elective OHE, by evaluating both subjective (CMPS-SF) and objective parameters (cortisol, heart rate, rectal temperature, NLR, PLR, and SII). We hypothesized that preoperative administration of meloxicam or firocoxib would reduce postoperative pain and systemic inflammatory responses compared to no preoperative NSAID treatment.

MATERIALS AND METHODS

Study design

This study was designed as a randomized controlled clinical trial. The study was conducted between January and April 2023. The general clinical status of the dogs, including general appearance, rectal temperature, heart rate, respiratory rate, and mucous membrane color, was assessed during the preoperative evaluation. Transabdominal ultrasonography was performed to detect any abnormalities of the genital tract or signs of pregnancy. Additionally, vaginal cytology was used to determine the stage of the estrous cycle.

Inclusion criteria required that dogs to be physiologically healthy, non-pregnant, non-lactating, not in the follicular phase of the estrous cycle, and free from any analgesic or corticosteroid treatment within the past four weeks.

A total of 30 clinically healthy female dogs scheduled for elective ovariohysterectomy were enrolled in the study. Informed consent was obtained from all dog owners. The dogs were aged between 9 and 44 months and weighed between 5.5 and 35.3 kg. The study population consisted of various breeds, with Golden Retrievers being the most represented (n=14), followed by medium-sized mixed-breed dogs (n=6). Additional breeds included Terriers (n=2), Kangals (n=2), and one dog each from the following breeds: Labrador Retriever, Yorkshire Terrier, Staffordshire Terrier, English Pointer, English Setter, and Boxer. Dogs were randomly assigned into three equal-sized groups (n=10 per group) stratified by body size: a firocoxib-treated group, a meloxicam-treated group, and a control group.

Anesthetic and surgical procedure

Food and water were withheld for at least 6 hours prior to surgery in all dogs. The firocoxib and meloxicam groups received their respective analgesic treatments 1 hour before anesthesia induction. All dogs were allowed to rest for approximately 30 minutes prior to, and 15 minutes after anesthetic induction in the recovery room.

Firocoxib was administered orally at a dose of 5 mg/kg (Previcox, Boehringer Ingelheim, Germany) to the firocoxib group. Dogs in the meloxicam group received 0.2 mg/kg meloxicam via subcutaneous injection (0.5%, Bavet Meloxicam, Bavet, Türkiye). The control group did not receive any anti-inflammatory drugs prior to ovariohysterectomy (OHE).

All dogs were premedicated with intramuscular xylazine at 1.5 mg/kg (Rompun 2%, Bayer, Türkiye). Anesthesia was induced using intramuscular ketamine at 7 mg/kg (Ketakontrol 10%, Doğa İlaç, Türkiye). An intravenous catheter was placed into the cephalic vein of the antebrachium, and a 0.9% saline solution was administered at a rate of 10 mL/kg/h during surgery.

A standard ventral midline OHE procedure was performed in all animals by the same two experienced veterinarians, each with over 10 years of clinical experience. For each patient, the incision length and duration of surgery (from the initial incision to final skin closure) were recorded.

Postoperative care and monitoring

Following surgery, all dogs were admitted to the postoperative care unit and monitored for 24 hours. Amoxicillin-clavulanic acid was administered intramuscularly at a dose of 10 mg/kg (Synulox, Haupt Pharma, Italy) once daily for five consecutive days. Monitoring for potential postoperative complications continued for 10 days following ovariohysterectomy (OHE). Additionally, heart rate and rectal temperature were recorded at 1, 2, 4, and 24 hours postoperatively in all animals.

Serum cortisol and inflammatory hematological parameters

Blood samples were collected from the cephalic vein of the antebrachium at 1 hour preoperatively and at 1, 2, 4, and 24 hours postoperatively to determine serum cortisol levels. Immediately after collection, samples were centrifuged at 3000 × g for 10 minutes, and serum was separated for analysis. Cortisol concentrations were measured using a fluorescent immunoassay analyzer (Wondfo Finecare, FIA Meter Plus, China), following the manufacturer's standard protocol. Each sample was processed individually, with a total analysis time of 15 minutes per sample.

Additional blood samples were collected into EDTA-coated tubes at 1 hour preoperatively and 24 hours postoperatively for complete blood count (CBC) analysis. CBCs were performed using an automated hematology analyzer (VH5A, Hasvet, Türkiye). Based on the CBC results, the following inflammatory indices were calculated:

- Neutrophil-to-lymphocyte ratio (NLR): calculated as the neutrophil count ($\times 10^9$/L) divided by the lymphocyte count ($\times 10^9$/L).
- Platelet-to-lymphocyte ratio (PLR): calculated as the platelet count ($\times 10^9$/L) divided by the lymphocyte count ($\times 10^9$/L).
- Systemic immune-inflammation index (SII): calculated as (neutrophil count × platelet count) / lymphocyte count (all in $\times 10^9$/L).

Postoperative pain assessment

Pain assessment was conducted by two veterinarians who were blinded to the treatment groups and trained in clinical pain evaluation. All assessments were conducted by mutual consensus of the assessors. Pain was scored using CMPS-SF at 1 hour preoperatively and at 1, 2, 4, and 24 hours postoperatively, as described by Reid et al. (2007). According to the scale's guidelines, rescue analgesia is recommended if the total score is ≥6 on the first assessment or ≥5 on the second assessment following surgery (Reid et al., 2007).

Tolfenamic acid was administered to any dog with a CMPS-SF score exceeding the rescue threshold at 1 hour postoperatively, regardless of group assignment. In addition, to ensure ethical pain management, all dogs in the control group received tolfenamic acid at 4 hours postoperatively, irrespective of pain scores. This approach aligns with veterinary ethical standards and aims to avoid untreated postoperative discomfort in animals not receiving preoperative NSAIDs.

Statistical analysis

All statistical procedures were carried out using IBM® SPSS Statistics 20, with data normality assessed via the Shapiro–Wilk test. One-way ANOVA was used for variables such as age, body weight, surgery duration, and incision length. Repeated measures ANOVA compared heart rate, rectal temperature, CMPS-SF scores, serum cortisol levels, and hematological parameters within each time point and among the three treatment groups. One-way ANOVA tests determined differences among groups, and Dependent Samples T-test was used to compare time points. Scheffe's post-hoc test identified groups responsible for differences, Fisher's exact test was used to analyze the need for rescue analgesia. Results were expressed as the mean accompanied by the standard error of the mean (SEM), with a p-value less than 0.05 considered indicative of statistical significance.

Ethical approval

The Balikesir University Animal Care Committee approved all procedures in this experiment (Reference Number: 2022/8-7 and date of approval: 27.10.2022).

RESULTS

In this study, dogs with an average age of 19.27±1.82 months had an average body weight of 19.42±1.41 kg. Intergroup comparisons for age and body weight demonstrated no statistically significant differences ($p > 0.05$). The mean duration of surgery was 12.70±0.86 min in all groups. This duration was 14.1±1.57 min in the meloxicam group, 10.8±1.27 min in the firocoxib group, and 13.2±1.55 min in the control group). There were no significant differences ($p>0.05$) in surgical duration among the groups. Furthermore, no statistically significant difference was observed in incision length (cm) among the meloxicam (5.30±0.34), firocoxib (4.71±0.20), and control (5.10±0.20) groups ($p>0.05$; Table 1).

Table 1. Comparison of general clinical parameters (mean ± SEM) including rectal temperature, heart rate, respiratory rate, and mucous membrane color in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control) before and after elective ovariohysterectomy.

Variables	Meloxicam (n=10)	Firocoxib (n=10)	Control (n=10)	Overall (n=30)
Age (month)	16.00±2.90	22.70±3.90	19.10±2.48	19.27±1.82
Body weight (kg)	19.61±2.68	16.95±1.84	21.42±2.56	19.41±1.41
Surgical duration (min)	14.10±1.57	10.80±1.27	13.20±1.55	12.70±0.86
Incision length (cm)	5.30±0.34	4.71±0.20	5.10±0.20	5.40±0.15

Although no significant difference in rectal temperature was found between the treatment groups, a time-dependent effect was observed ($p<0.05$). All groups experienced their lowest rectal temperature value (36.65±0.2 °C) at 1 hour postoperatively ($p<0.05$). The temperature gradually increased at 2 and 4 hours postoperatively and returned to preoperative levels (38.85 ± 0.09 °C) by 24 hours postoperatively (Table 2). Similarly, time-dependent significance (p<0.05) was observed in heart rate without significance among groups. The lowest heart rate (104.51 ± 7.7 bpm) was recorded at postoperative1 hour (p<0.05). The heart rate increased at postoperative 2 hour (p>0.05) and remained elevated at postoperative 4 and 24 hour (Table 3).

Table 2. Time-dependent changes in rectal temperature (°C; mean ± SEM) measured preoperatively and at 1, 2, 4, and 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control).

	Meloxicam (n=10)	Firocoxib (n=10)	Control (n=10)	Overall (n=30)
Preoperative	38.90±0.12	38.77±0.26	38.55±0.14	38.74 ±0.19 [a]
Postoperative 1 h	36.84±0.36	36.10±0.36	37.00±0.28	36.65±0.2 [b]
Postoperative 2 h	37.87±0.24	37.24±0.43	37.37±0.27	37.52±0.17 [c]
Postoperative 4 h	38.52±0.22	38.02±0.23	38.42±0.21	38.13±0.13 [d]
Postoperative 24 h	39.11±0.14	38.51±0.16	38.86±0.13	38.85±0.09 [a]

a, b: The difference between the means with different letters in the same column is statistically significant (p<0.05).

Table 3. Time-dependent changes in heart rate (beats per minute, bpm; mean ± SEM) measured preoperatively and at 1, 2, 4, and 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control).

	Meloxicam (n=10)	Firocoxib (n=10)	Control (n=10)	Overall (n=30)
Preoperative	133.5±6.98	121.71±9.86	124.44±6.05	127.19±4.25 [a]
Postoperative 1 h	94.9±12.70	104.62±9.61	115.11±13.57	104.51±7.75 [b]
Postoperative 2 h	134.80±10.96	110.57±14.93	120.44±12.28	123.30±7.18 [a]
Postoperative 4 h	131.58±8.62	116.00±12.18	130.66±9.16	126.62 ± 5.64 [a]
Postoperative 24 h	128.6±8.05	106.01±7.19	132.44±6.71	123.18 ± 4.68 [a]

a, b: The difference between the means with different letters in the same column is statistically significant (p<0.05).

The CMPS-SF scores demonstrated a significant time-dependent effect (p<0.05); however, no significant differences were observed between treatment groups. At 1 hour preoperatively, the mean CMPS-SF scores were 1.1 ± 0.43 in the meloxicam group, 0.75±0.36 in the firocoxib group, and 1.88±0.53 in the control group. It significantly increased at postoperative 1 hour (p < 0.05). Two dogs in the firocoxib group and one dog in the control group had a CMPS-SF score higher than 6, received rescue analgesia at this time point. Hence, two dogs were removed from further analysis. The CMPS-SF score remained elevated at postoperative 2 and 4 hours. Similar to rectal temperature and heart rate, CMPS-SF score returned to preoperative period values at postoperative 24 hour (p>0.05; Figure 1).

Serum cortisol levels showed significant individual variation ranging from 25.73 nmol/l to 441.66 nmol/l at 1 hour preoperatively. Although significant time-dependent changes were observed in cortisol concentrations (p<0.05), no statistically significant differences were found among the treatment groups. The average serum cortisol level was 99.69±19.18 nmol/l, with levels of 123.31±31.80 nmol/l in the meloxicam group, 121.30±35.56 nmol/l in the firocoxib group, and 71.45±33.52 nmol/l in the control group.

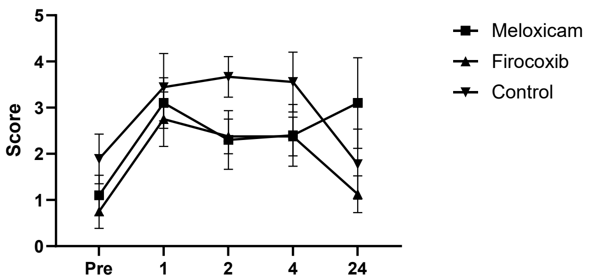

Figure 1. Time-dependent changes in pain scores (mean ± SEM) assessed preoperatively and at 1, 2, 4, and 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control), based on the short form of the Glasgow Composite Measure Pain Scale (CMPS-SF).

Serum cortisol levels at postoperative 1 hour increased (p < 0.05) approximately four-fold (408.99±35.72 nmol/l). Furthermore, serum cortisol levels peaked (p < 0.05) at nearly five-fold (530.2±41.17 nmol/l) at postoperative 2 hour. Afterwards, serum cortisol levels (429.37±36.04 nmol/l) at postoperative 4 hour had decreased (p < 0.05) to similar levels at postoperative 2 hour. While the serum cortisol levels of the meloxicam groupwere not significantly different (p < 0.05) from preoperative levels at postoperative 4 hour, this similarity was not observed in the firocoxib and control groups and still remained elevated at postoperative 4 hour. Serum cortisol levels (97.58±9.69 nmol/l) returned ($p < 0.05$) to preoperative levels at postoperative 24 hour (Figure 2).

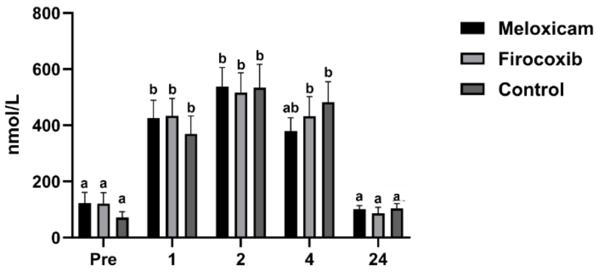

Figure 2. Serum cortisol concentrations (mean ± SEM) measured preoperatively and at 1, 2, 4, and 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control)
a-b: Significant differences between groups within the same time point and between time points within the same group ($p < 0.05$).

The NLR (Figure 3), PLR (Figure 4), and SII (Figure 5) values showed time-dependent alteration at postoperative 24 hour compared to those at preoperative 1 hour. However, the difference was not statistically significant ($p > 0.05$). The NLR and SII were higher ($p < 0.05$) in the control group than meloxicam and firocoxib groups. Despite variations among the groups, the differences in PLR were not statistically significant ($p > 0.05$).

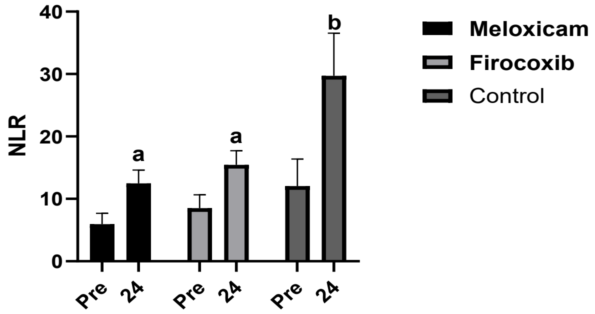

Figure 3. Neutrophil-to-lymphocyte ratio (NLR; mean ± SEM) measured preoperatively and at 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control)
a-b: Significant differences between groups within the same time point (p<0.05)

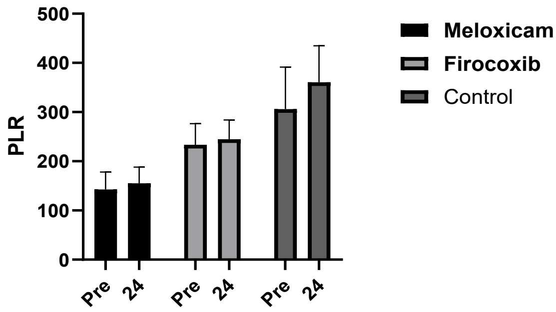

Figure 4. Platelet-to-lymphocyte ratio (PLR; mean ± SEM) measured preoperatively and at 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control)

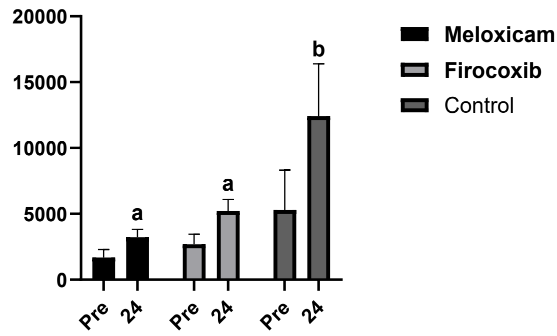

Figure 5. Systemic immune-inflammation index (SII; mean ± SEM) measured preoperatively and at 24 hours postoperatively in dogs receiving meloxicam, firocoxib, or no preoperative NSAID (control)
a-b: Significant differences between groups within the same time point (p<0.05)

DISCUSSION

In the control group, although preoperative analgesia was not administered, rescue analgesia (tolfenamic acid) was provided postoperatively when required; at this time point, one dog exhibited a CMPS-SF score exceeding 6. Therefore, the CMPS-SF scores and serum cortisol levels suggested that dogs undergoing OHE in this study did not experience marked or prolonged pain-related stress. However, the CMPS-SF score was higher especially within the first 4 hours following surgery. Our results are consistent with previous study that OHE causes acute and short-term postoperative pain (Gaynor and Muir, 2014). Although CMPS-SF scores were relatively higher in the control group at 4 hours postoperatively, the difference between the control and treatment groups was not statistically significant. Consistent with our results, Zanuzzo et al. (2015) found higher pain scores at postoperative 4 hour in dogs undergoing OHE. The absence of a notable distinction in pain scores between the control and treatment groups during the postoperative phase. There is a strong probability that our results regarding minimal incision length and operation period indirectly express minimal surgical intervention. These results might be linked to the minimal surgical intervention performed by an experienced veterinarian

(Kum et al., 2013), the potential analgesic effect of ketamine (Morgan and Curran, 2012; Nenadović et al., 2017; Slingsby and Waterman-Pearson, 2001).

Due to ethical considerations, the number of animals in the experimental groups in the present study was kept limited, as similarly reported in previous studies (Slingsby and Waterman-Pearson, 2001; Camargo et al., 2011; Teixeira et al., 2013; Karakaya Bilen et al., 2025). Limitations of our study include the relatively small sample size in each group and animals that received rescue analgesia based on CMPS-SF thresholds were excluded from further statistical analysis. This exclusion, although ethically necessary, further reduced the sample size, particularly in the firocoxib and control groups, and may have affected the statistical power to detect differences, especially cortisol levels, during the early postoperative period. Despite these limitations, the study provides meaningful insights into the analgesic and anti-inflammatory effects of preoperative NSAID administration in dogs undergoing OHE.

The postoperative analgesic effect of meloxicam has been frequently evaluated in previous studies. Zanuzzo et al. (2015) observed a reduction in pain scores starting from 1 hour postoperatively in the meloxicam group compared to the placebo group. Teixeira et al. (2013) found no significant difference in pain scores between meloxicam and ozone therapy in dogs undergoing elective OHE. Another study reported that the analgesic effects of meloxicam and carprofen were comparable (Leece et al., 2005). Similarly, Gruet et al. (2013) reported no difference in postoperative pain scores between robenacoxib and meloxicam following soft tissue surgery. In our study, both meloxicam and firocoxib groups demonstrated effective postoperative analgesia based on CMPS-SF scores and normalization of cortisol levels by 24 hours. However, although firocoxib was generally effective in postoperative pain control, the requirement for rescue analgesia in two dogs within this group suggests that its analgesic efficacy may not be sufficient in all individuals. In contrast, none of the dogs in the meloxicam group required additional analgesia, and a more pronounced reduction in serum cortisol was observed in this group at 4 hours postoperatively. These findings may indicate a more consistent or prolonged analgesic effect of subcutaneous meloxicam compared to oral firocoxib. Consistent with our results, Camargo et al. (2011) reported that while firocoxib showed better analgesic efficacy than butorphanol during the first three postoperative hours, no significant difference was observed at later time points, and two of thirteen dogs in the firocoxib group required rescue analgesia. Studies on various analgesic protocols for dogs undergoing OHE have demonstrated that plasma cortisol levels rise between 30 and 240 minutes after anesthesia induction, depending on the surgical technique, anesthesia, and analgesic regimen (Devitt et al., 2005; Kim et al., 2012; Mastrocinque et al., 2012; Mastrocinque and Fantoni, 2003). Gruet et al. (2013) investigated the effect of meloxicam and robenacoxib on plasma cortisol levels and cortisol levels increased approximately two-fold during the postoperative period compared to the preoperative period. Postoperative higher plasma cortisol levels reduced at postoperative 8 hours. Yilmaz et al. (2014) found that higher cortisol levels at 30 minutes, 1 hour, and 2.5 hours post-surgery in the placebo group compared to the meloxicam and flunixin meglumine groups in dogs undergoing OHE. Moreover, cortisol levels increased during the postoperative period and returned to preoperative values by 12 hours postoperatively.

In a different study (Nenadović et al., 2017) comparing carprofen and placebo, cortisol levels significantly increased at 0.5 and 4 hours in dogs undergoing OHE compared to preoperative levels. However, the authors did not determine significant difference in cortisol levels between the groups. Cortisol levels peaked at postoperative 2 hours after OHE,reduced at postoperative 4 hours, and decreased to preoperative period levels at postoperative 24 hours in this study. In our study, the earlier decrease in serum cortisol levels compared to previous studies might be explained by minimal invasive surgery by experienced veterinarians. The time-dependent alteration of cortisol concentration in our study is consistent with previous studies reporting 2 or 3-fold increase at postoperative 2 to 4 hours (Kona-Boun et al., 2006; Nenadović et al., 2017; Tsai et al., 2013). Furthermore, the decrease in serum cortisol levels at postoperative 4 hour was more pronounced in the meloxicam group. The cortisol level at postoperative 4 hour did not show a significant difference compared to the preoperative levels in this group. No similar change was observed in the firocoxib and control groups. It appears that subcutaneous meloxicam may offer a more effective postoperative analgesic effect than oral firocoxib, especially considering the lack of need for rescue analgesia based on the CMPS-SF in the meloxicam group. Heart rate and rectal temperature values did not differ significantly between the groups before the OHE procedure. The average rectal temperature of the dogs (38.74 ± 0.19) was within the reference range (38.4 ± 0.6, Steeve et al., 2005). However, the average heart rate (127.19 ± 4.25) was above the reportedreference range (87±22, Steeve et al., 2005). Increased heart rate before surgery has been reported in other studies (Akkuş and Ekici, 2023; Kalchofner Guerrero et al., 2016; Srithunyarat et al., 2016) and is thought to be associated with preoperative fear and excitement (De Souza et al., 2018). During postoperative assessments, heart rate decreased at 1 hour and normalized by 2 hours, whereas rectal temperature exhibited a decline at 1 hour and returned to normal levels within 24 hours. This observed decrease could be attributed to the ongoing pharmacological effects of anesthetic agents during the postoperative phase (Díaz and Becker, 2010). Similar to our study, Tsai et al., (2013) reported no significant differences in heart rate and rectal temperature after OHE among the meloxicam, lidocaine, and meloxicam + lidocaine groups. In contrast to our study, Hu et al. (2017) reported that the meloxicam and tolfenamic acid groups had lower heart rates at postoperative 4 and 6 hours compared to the control group. It is clear that these differences are not only pain-related, but can also be influenced by factors such as fear, stress, anaesthesia and pharmacological interventions. Therefore, the absence of temporal and intergroup differences may be attributed to these multifactorial influences.

Pain relief for pets in veterinary practice is not optimal and making pain management a real challenge due to the difficulty in recognizing pain in non-verbal patients. When the studies on postoperative pain management in dogs are analyzed, it is apparent that some studies do not include a control group (Hu et al., 2017; Nunamaker et al., 2014; Teixeira et al., 2013). However, similar to our study, a control group was established to explore the varied effects of the analgesics (Hu et al., 2017; Nunamaker et al., 2014; Teixeira et al., 2013; Grandemange et al., 2007; Guerrero et al., 2016; Ugwu et al., 2017; Zanuzzo et al., 2015). In our study, a COX-2 inhibitor, tolfenamic acid was administered to the control group as rescue analgesia at postoperative 4 hours based on CMPS-SF (Grandemange et al., 2013; Hu et al., 2017; Kalchofner Guerrero et al., 2016; Nunamaker et al., 2014; Teixeira et al., 2013; Ugwu et al., 2017; Zanuzzo et al., 2015). Rescue analgesia was administered to decrease potential postoperative pain and ensure animal welfare during periods without pain assessment. Tolfenamic acid was selected for its rapid onset of action and relatively short ($t_1/_2 \approx 6.5$ hours in dogs) half-life (Hanson and Madison, 2008), which minimizes pharmacokinetic interference with the long-acting NSAIDs used in the treatment groups (meloxicam and firocoxib). This strategic selection allowed for pain control in the control group without introducing prolonged anti-inflammatory effects that could confound comparative analyses. Therefore, considering that NSAIDs with a short half-life were administered to the control group as rescue analgesia, it is appropriate to include this group in the comparison of postoperative pain scores and serum cortisol levels at the 24th hour following OHE. We noted that NLR and SII values were significantly higher in the control group at postoperative 24 hour. NLR, PLR, and SII are used as markers of stress and systemic inflammatory responses in mammals (Espadas-González et al., 2023). Only one study evaluating these parameters in dogs undergoing OHE (Espadas-González et al., 2023). Based on our literature review, our study is the first to assess the impact of different analgesic agents on these parameters in dogs. In the study by Espadas-González et al. (2023), an increase in NLR, PLR, and SII values was observed between 1 and 24 hours postoperatively compared to preoperative values. Consistent with previous reports, our study showed a significant increase in NLR and SII in all dogs at postoperative 24 hours compared to preoperative values. Although PLR was previously reported to rise postoperatively (Espadas-González et al., 2023), the lack of significant difference among the groups in our study may reflect individual platelet variability or a lesser sensitivity of PLR to acute-phase analgesic responses in canine surgical models. The analgesics administration before the onset of a painful stimuli has been reported to result in higher tissue levels, thereby enhancing the efficacy of the treatment against local inflammation (Gurney, 2012; Lascelles et al., 1998). Although the control group did not receive preemptive analgesia, the administration of a short-acting rescue analgesic postoperatively (tolfenamic acid) likely provided limited pain relief, which may have masked some intergroup differences but did not alter the overall inflammatory and stress responses observed at 24 hours.

CONCLUSION

Our findings indicate that preoperative administration of meloxicam provided consistent and effective analgesia, while firocoxib showed variable efficacy in healthy dogs undergoing ovariohysterectomy. Pain, as measured by CMPS-SF scores and serum cortisol levels, peaked during the early postoperative hours but returned to baseline by 24 hours in all groups. However, the requirement for rescue analgesiain two dogs from the firocoxib group suggests that its analgesic effect may not be sufficient in all individuals. These findings suggest that while both meloxicam and firocoxib reduced systemic inflammatory markers such as NLR and SII at 24 hours, fewer instances of rescue analgesia were required in the meloxicam group, indicating a potential advantage in analgesic efficacy. Overall, the results highlight the importance of both the timing and selection of NSAID administration and support the inclusion of extended postoperative monitoring, particularly at the 24th hour, to evaluate the effectiveness of analgesic protocols in dogs undergoing OHE.

Acknowledgement

The authors would like to thank Dr. Melike Çetin and Dr. Çetin Bozkurt.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Author Contributions

Plan, design: BG**; Material, methods and data collection:** OAS, BO, AAE, BG**; Data analysis and comments:** BO, AAE**; Writing and corrections:** OAS, BO, AAE, BG

Funding

This project was supported for master thesis by Balıkesir University Scientific Research Projects Unit (Reference No: 2023/004).

Ethical Approval

Institution: The Balikesir University Animal Care Committee

Date: 27.10.2022

Approval no: 2022/8-7

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