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Comparative Evaluation of Postoperative Analgesia and Cardiorespiratory Effects of Meloxicam and Methadone in Canine Ovariohysterectomy

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ABSTRACT

This randomized controlled study evaluated the comparative efficacy of meloxicam and methadone on postoperative analgesia and cardiorespiratory parameters in 24 female dogs undergoing ovariohysterectomy (OHE). After premedication with acepromazine (0.05 mg/kg) and morphine (0.05 mg/kg) intramuscularly, anesthesia was induced intravenously with propofol at 6 mg/kg, titrated to effect. The dogs were maintained on isoflurane and 100% oxygen at a rate of 100 ml/kg/min. The dogs, then, underwent OHE with continuous monitoring of physiologic variables. Immediately after the final skin suture, the dogs were randomly assigned to one of three treatments: saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8), all administered IV. Postoperatively, cardiorespiratory parameters were recorded. Pain was assessed using three pain scoring scales. Inflammatory/stress markers (cortisol, glucose, lactate, TNFα, IL-1β) were also measured. The results showed that methadone-treated dogs exhibited lower heart rates and required less rescue analgesia compared to the SAL. The Glasgow Composite Pain Scale-Short Form was lower at 30 minutes in the MET compared to the MEL. Dogs in the MEL and MET showed some benefits in modulating inflammatory markers, which were more pronounced in the MEL. In conclusion, methadone provided more effective postoperative pain control and contributed to better cardiorespiratory stability in canine ovariohysterectomy compared to placebo and meloxicam.

Introduction

Ovariohysterectomy (OHE) is one of the most common surgeries performed on female dogs, primarily for population control, prevention of reproductive disease, and treatment of a variety of uterine and ovarian pathologies.[1] Although OHE is considered routine, there is moderate to severe postoperative pain associated with most surgical procedures, which requires analgesic strategies to ensure animal welfare and faster recovery, and to prevent chronic pain development.[2,3] The management of postoperative pain in veterinary medicine recommends a multimodal approach.[4] Most multimodal approaches entail the use of non-steroidal anti-inflammatory drugs (NSAIDs) or opioids.[5]

Meloxicam is a selective cyclooxygenase-2 (COX-2) inhibitor with anti-inflammatory, analgesic, and antipyretic properties. It is one of the most commonly prescribed NSAIDs by veterinarians.[6] Overall, meloxicam is effective for treating mild to moderate pain and inflammation, and due to its long duration of action, it is advantageous for managing postoperative pain.[7] As with all NSAIDs, meloxicam has potential side effects, and is of particular concern in pregnant and

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lactating animals.[8] Methadone is a synthetic μ-opioid receptor agonist that has similar analgesic properties as other opioids, but is typically preferred for moderate to severe pain in dogs.[9] Its advantages include its rapid onset of action, relatively long duration of action, and minimal sedation effects compared to other opioids like morphine.[10] Methadone has also been shown to possess N-methyl-D-aspartate (NMDA) receptor antagonist properties, which can enhance its analgesic effect by preventing central sensitization.[11] Opioids can also cause cardiorespiratory depression; this effect, however, is relatively minimal at clinically relevant doses.[12,13]

Given the unique pharmacologic properties of meloxicam and methadone, this study was designed to compare the postoperative analgesic efficacy and physiological effects of meloxicam, methadone, and placebo in dogs undergoing OHE. It was hypothesized that both meloxicam and methadone would demonstrate superior analgesia compared to placebo, and that methadone would produce even more analgesia and fewer physiologic alterations and adverse effects than meloxicam.

Materials and Methods

Animals

A total of twenty-four healthy, mixed-breed female dogs with similar weights and ages were used in the study. The dogs were all ASA physical status I or II, with a Body Condition Score (BCS) of 3-6 on a 9-point scale.[14] Before the study, each dog was individually housed in the faculty's kennel for 14 days, receiving anthelmintic treatments, free access to water, and twice-daily feeding. A 12-hour fast, with water withheld for 2 hours, was conducted before surgery. The Ethics Committee of Shahid Chamran University of Ahvaz approved this study (EE/402.20.4.84474/SCU.ac.ir).

Experimental Design and Procedure

The pre-anesthetic medications consisted of 0.05 mg/kg acepromazine (Neurotranq, Alfasan, Woerden, Holland) and 0.05 mg/kg morphine (Morphine Sulfate, 10 mg/ml, Darou Pakhsh, Tehran, Iran) intramuscularly. Fifteen minutes after premedication, a catheter was aseptically inserted into the cephalic vein, and Ringer's solution (Ringer, Shahid Ghazi Pharmaceutical Co., Iran) was infused at a rate of 5 ml/kg/hr. Approximately 15 minutes later, the animals received oxygen (100%) via flow-by for five minutes. Then, anesthesia was induced intravenously (IV) with propofol (Arufol, 10 mg/ml, Darou Darman Arang, Tehran, Iran) at 6 mg/kg, titrated to effect for endotracheal intubation. The dogs were then connected to an anesthetic machine and maintained on isoflurane (Isoflurane, Pirama Pharma Ltd., Telangana State, India) and 100% oxygen at a rate of 100 ml/kg/min. Heart rate (HR), respiratory rate (f_R), indirect blood pressure (BP), pulse oximetry (SpO_2), end-tidal carbon dioxide ($ETCO_2$), and rectal temperature (RT) were continuously monitored using a multiparametric monitoring device (Burtons, PM-9000Vet, UK). Warm water blankets were used to maintain body temperature between 37 and 38 °C.

Ovariohysterectomy was done through a midline laparotomy on all dogs as described elsewhere.[15] Physiological parameters guided intraoperative pain management, and if heart rate or mean arterial pressure (MAP) increased by 20% or more from the baseline, dogs received 1 μg/kg fentanyl (IV; one to two doses maximum). If HR or MAP did not return to baseline, fentanyl IV infusion was started at 5 μg/kg/hr.

In the current study, the dogs randomly (www.randomizer.org) received one of three treatments: saline (SAL, n = 8), meloxicam (Melexivet 2%, Razak Laboratories, Tehran, Iran) at a dose of 0.2 mg/kg (MEL, n = 8)[12] and methadone (Methadone, 5 mg/ml, Darou Pakhsh, Iran) at a dose of 0.2 mg/kg (MET, n = 8)[10] IV, immediately after the final skin suture.

After the surgery, infusion of Ringer's solution was discontinued, and oxygen was given through the endotracheal tube until the swallow reflex returned. All dogs received postoperative cefazolin (22 mg/kg, IM) every 12 hours for three days. If the postoperative pain was greater than 8 on the University of Melbourne Pain Scale (UMPS) or 5/20 or 6/24 on the Glasgow Composite Pain Scale-Short Form (GCPS-SF), a dose of morphine (0.05 mg/kg, IM) was administered as rescue analgesia. If a dog received rescue analgesia for pain requiring more than two doses, it was excluded from the study.

Cardiorespiratory Variables

HR, BP, f_R, and RT were recorded 5 min prior to premedication to serve as baseline (T0). Using the same values listed above as parameters, SpO_2 and $ETCO_2$ were to be recorded at the following surgical events: skin incision (T1), *linea alba* incision (T2), ligation of ovarian pedicles (T3), and skin closure (T4). Postoperatively, HR, BP, f_R, and RT were recorded at 15, 30, 45, 60, 75, 90, 120 minutes, and hourly for 6 hours post-surgery.

Postoperative Pain Assessment

Pain was assessed using three validated methods: the Colorado State University Canine Acute Pain Scale (CSU-UAPS), the UMPS, and the GCPS-SF. Assessments were performed at baseline (before anesthesia), immediately after surgery (0 minutes), and then at 15, 30 minutes, and subsequently at 1, 2, 3, 4, and 6 hours postoperatively. The data were recorded and measured by the same investigator.

Biochemical Analyses

Blood samples were collected from the jugular vein to measure cortisol, glucose, and lactate levels. Samples were taken before anesthesia, at 30, 60 minutes, and then at 2, 3, 4, 5, 6, 12, and 24 hours post-anesthesia. For tumor necrosis factor-alpha (TNFα) and interleukin-1 beta (IL-1β), samples were collected 1 hour before anesthesia and 4, 12, and 24 hours post-anesthesia. All blood samples were centrifuged, and the serum was separated and stored at -20 °C until biochemical analysis.

To determine the concentration of cortisol present in the serum, the enzyme-linked immunosorbent assay (ELISA) method was used, utilizing the Accubind ELISA (Monobind, USA) and the Microwells cortisol assay kit. Glucose and lactate concentrations were determined using the Colorimetric, Enzymatic, Endpoint method (Man Company, Iran). TNFα and IL-1β were measured using a commercial kit with the Sandwich-ELISA method (Sunlong Biotech, China).

Statistical Analysis

The collected data were analyzed using IBM SPSS Statistics for Windows (Version 22.0, Armonk, NY: IBM Corp.) both descriptively and analytically. The average and standard error (SE) of the mean were used to describe the data. The repeated measures ANOVA and one-way ANOVA, followed by the Tukey test, were used to compare three groups for quantitative data. The Friedman and Kruskal-Wallis tests were used for qualitative data. A significance level of $p < 0.05$ was considered.

Results

There were no statistically significant differences ($p > 0.05$) among the groups in terms of key demographic and procedural characteristics, including body weight, BCS, age, duration of anesthesia, and duration of surgery (Table 1). RT, SPO_2, and $ETCO_2$ were all within normal ranges, with no significant difference among groups ($p > 0.05$).

Physiologic Variables during Surgery

Analyses of HR during surgery demonstrated a significant effect of time on HR. Time significantly affected HR ($p = 0.002$), with a trend toward significance for Group SAL ($p = 0.02$). No significant differences were observed between groups (all $p > 0.05$). A significant group effect for systolic arterial pressure (SAP) was observed during surgery ($p = 0.01$). Post-hoc test identified significant differences at time 1 and 3 ($p \leq 0.02$, group MEL *vs.* SAL and MET), and 2 ($p = 0.03$, Group MET *vs.* SAL and MEL). For diastolic arterial pressure (DAP), a significant difference was detected at time 4 ($p = 0.02$, Group SAL vs. MET). For mean arterial pressure (MAP), significant effects were demonstrated for time ($p = 0.004$) and for the interaction between time and group ($p < 0.001$). A significant decline in MAP over time was specifically observed in group MET ($p = 0.002$). Also, at time 1 [group MET with SAL and MEL ($p \leq 0.001$) and SAL with MEL ($p = 0.01$)] and 4 [group MET with SAL ($p = 0.004$) and MEL ($p = 0.03$)] there was a difference between the three groups. f_R showed a significant time effect ($p = 0.015$) with a significant difference at time 2 ($p = 0.015$, group SAL *vs.* MEL and MET) (Table 2).

Physiologic Variables after Surgery

HR analysis yielded significant results for time ($p < 0.001$), group ($p = 0.028$), and the interaction between time and group ($p = 0.02$). The trend of HR changes in group SAL ($p = 0.004$) was significant. In the SAL, the time before surgery differed from time 0 and 15 minutes after surgery ($p \leq 0.046$). Also, at times 0 [group SAL with MET ($p \leq 0.01$)], 15, 30, and 60 minutes [group SAL with MET ($p \leq 0.002$) and group MEL with MET ($p \leq 0.04$)], there was a significant difference between the three groups (Figure 1).

For SAP, the time factor ($p < 0.001$) had a significant impact. The trend of SAP changes in group MEL was significant ($p \leq 0.001$). In the MET, the baseline value was significantly different from other time points ($p \leq 0.02$). A comparison of DAP in three groups over time showed that time ($p \leq 0.001$) and the interaction effect of time and group ($p = 0.03$) had a significant effect on this index. In group MEL, the time before surgery was different from the time of surgery completion, 15, 30, 45, 75, and 90 minutes, 2, 4, 5, and 6 hours ($p \leq 0.01$) after surgery. For MAP, it was shown that time ($p \leq 0.001$) had a significant effect on this index. In the MEL, the time before surgery was different from the time of surgery completion, 15, 30, 45, 75, and 90 minutes, and 2, 3, 4, 5, and 6 ($p \leq 0.01$) after surgery. Additionally, there was no difference between

Table 1. Signalments for dogs received intravenous saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8) immediately after ovariohysterectomy.

	Body weight (kg)	BCS (1-9)	Age (months)	Duration of Anesthesia (minutes)	Duration of Surgery (minutes)
SAL	17.90 ± 01.98	03.75 + 00.37	14.38 ± 01.93	86.88 ± 11.89	49.88 ± 03.06
MEL	17.95 ± 01.48	03.63 ± 00.26	11.25 ± 01.35	90.75 ± 08.18	52.00 ± 00.74
MET	23.63 ± 01.73	04.25 ± 00.16	16.25 ± 01.67	77.75 ± 08.26	49.38 ± 05.00
***p* value**	0.051	0.12	0.12	0.62	0.94

Table 2. Mean ± standard error of physiologic parameters [heart rate (HR), systolic, diastolic, and mean arterial blood pressure (SAP, DAP, and MAP), and respiratory rate (f_R)] at baseline, skin incision (T1), *linea alba* incision (T2), ligation of ovarian pedicles (T3), and skin closure (T4) in dogs received intravenous saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8) immediately after ovariohysterectomy.

	Group	Baseline	Time 1	Time 2	Time 3	Time 4
HR	SAL	89 ± 12^{Ba}	110 ± 10^{Ba}	108 ± 9^{Ba}	112 ± 5^{Ba}	130 ± 8^{Aa}
	MEL	102 ± 12^{Aa}	104 ± 9^{Aa}	110 ± 10^{Aa}	120 ± 9^{Aa}	133 ± 14^{Aa}
	MET	104 ± 5^{Aa}	98 ± 14^{Aa}	109 ± 4^{Aa}	100 ± 4^{Aa}	109 ± 5^{Aa}
SAP	SAL	126 ± 15^{Aa}	143 ± 10^{Aa}	104 ± 5^{Ab}	122 ± 8^{Aa}	115 ± 12^{Aa}
	MEL	108 ± 4^{Aa}	107 ± 1^{Ab}	105 ± 5^{Ab}	94 ± 6^{Ab}	115 ± 7^{Aa}
	MET	134 ± 6^{Aa}	113 ± 9^{Aa}	132 ± 10^{Aa}	133 ± 12^{Aa}	142 ± 9^{Aa}
DAP	SAL	59 ± 7^{Aa}	66 ± 5^{Aa}	53 ± 3^{Aa}	56 ± 4^{Aa}	56 ± 3^{Ab}
	MEL	57 ± 7^{Aa}	52 ± 3^{Aa}	56 ± 4^{Aa}	51 ± 6^{Aa}	65 ± 5^{Aab}
	MET	65 ± 5^{Aa}	63 ± 6^{Aa}	62 ± 5^{Aa}	62 ± 5^{Aa}	73 ± 3^{Aa}
MAP	SAL	78 ± 9^{Aa}	94 ± 5^{Aa}	66 ± 4^{Aa}	77 ± 4^{Aa}	78 ± 8^{Ab}
	MEL	75 ± 5^{Aa}	77 ± 1^{Ab}	74 ± 5^{Aa}	70 ± 5^{Aa}	86 ± 46^{Ab}
	MET	77 ± 5^{Ca}	49 ± 6^{Ec}	89 ± 9^{Ba}	74 ± 9^{CBDEa}	107 ± 7^{ABa}
f_R	SAL	20 ± 2^{Aa}	21 ± 2^{Aa}	20 ± 2^{Aa}	18 ± 1^{Aa}	17 ± 1^{Aa}
	MEL	20 ± 2^{Aa}	16 ± 2^{Aa}	15 ± 1^{Ab}	15 ± 1^{Aa}	16 ± 1^{Aa}
	MET	22 ± 4^{Aa}	17 ± 1^{Aa}	14 ± 1^{Ab}	17 ± 1^{Aa}	15 ± 1^{Aa}

Different capital letters indicate significant differences within rows (across time points). Different lowercase letters indicate significant differences within columns (across groups).

the three groups for SAP, DAP and MAP at any time ($p > 0.05$) (Figure 1).

For f_R, significant effects were found for time ($p < 0.001$) and time, and group interaction ($p = 0.03$), with a trend observed in group SAL ($p = 0.015$). A comparison of the f_R in three groups over time revealed that time ($p < 0.001$) and the interaction effect of time and group ($p = 0.03$) had a significant impact on this index. In group SAL, the time before surgery differed significantly from 3, 4, 5, and 6 hours after surgery ($p \leq 0.04$). There was also a significant difference between the three groups, MEL vs. SAL ($p = 0.001$) and MET ($p = 0.005$), at 6 hours after surgery (Figure 1).

Pain Scores and Rescue Analgesia

Within-group differences in the CSU, UMPS, and GCPS-SF were statistically significant over time ($p < 0.001$). Between-group differences were noted for GCPS-SF at 30 minutes ($p = 0.03$, group MEL *vs.* MET). No significant differences were identified for CSU or UMPS across groups (all $p > 0.05$) (Figure 2). The relative frequency of rescue analgesia in the groups SAL, MEL, and MET was 75%, 50%, and 25%, respectively. It was significantly lower in group MET than in SAL ($p = 0.07$), but there was no difference between SAL and MEL ($p = 0.3$) and MEL and MET ($p = 0.3$).

Inflammatory and Stress Markers

A comparison of cortisol levels showed that time ($p < 0.001$), group ($p = 0.01$), and the interaction of time and group ($p < 0.001$) had a significant effect on this index. In groups MEL and MET, time 1 differed from times 2, 3, 4, 5, 6, and 7 ($p \leq 0.008$). In the MEL, it was also significant at times 8 ($p = 0.006$) and 9 ($p = 0.02$) compared to time 1. At time 3 [group SAL with MEL ($p = 0.02$)], time 4 [group SAL with MEL ($p = 0.01$) and MET ($p = 0.001$), and MEL with MET ($p = 0.004$)], time 5, 6, 7 [group MET with SAL ($p = 0.01$) and MEL ($p \leq 0.02$)], and 8 [group SAL with MEL ($p = 0.008$) and MET ($p = 0.004$)], there was a difference between the groups. A comparison of glucose levels revealed that time had a significant effect on this index ($p < 0.001$). In group MEL, time 1 differed significantly from times 3, 4, 5, 6, 7, and 8 ($p \leq 0.04$). A comparison of lactate levels revealed that time had a significant effect on this index ($p < 0.001$). In group MEL, time 1 differed significantly from times 3, 4, 5, 6, 7, 8, and 9 ($p \leq 0.009$). In group MET, time 1 differed significantly from times 3, 4, 5, 6, and 7 ($p \leq 0.03$). Additionally, at time 3, a significant difference was observed between the SAL and MET groups ($p = 0.009$) (Figure 3).

A comparison of TNFα levels showed that time ($p < 0.001$), group ($p = 0.008$), and the interaction of time and group ($p < 0.001$) had a significant effect on this index. In groups MEL and MET, time 1 differed significantly from 2, 3, and 4 ($p \leq 0.04$). Also, at times 3 and 4, group SAL was significantly different from MEL ($p = 0.03$) and MET ($p \leq 0.003$). A comparison of IL-1β levels showed that time ($p < 0.001$) and the interaction effect of time and group ($p < 0.001$) had a significant effect on this index. In group MEL, time 1 differed significantly from times 3 and 4 ($p \leq 0.008$). In the group MET, time 1 differed from time 3 ($p = 0.02$). Additionally, at time 3, the group MET was significantly different from both SAL ($p = 0.002$) and MEL ($p = 0.01$) (Figure 4).

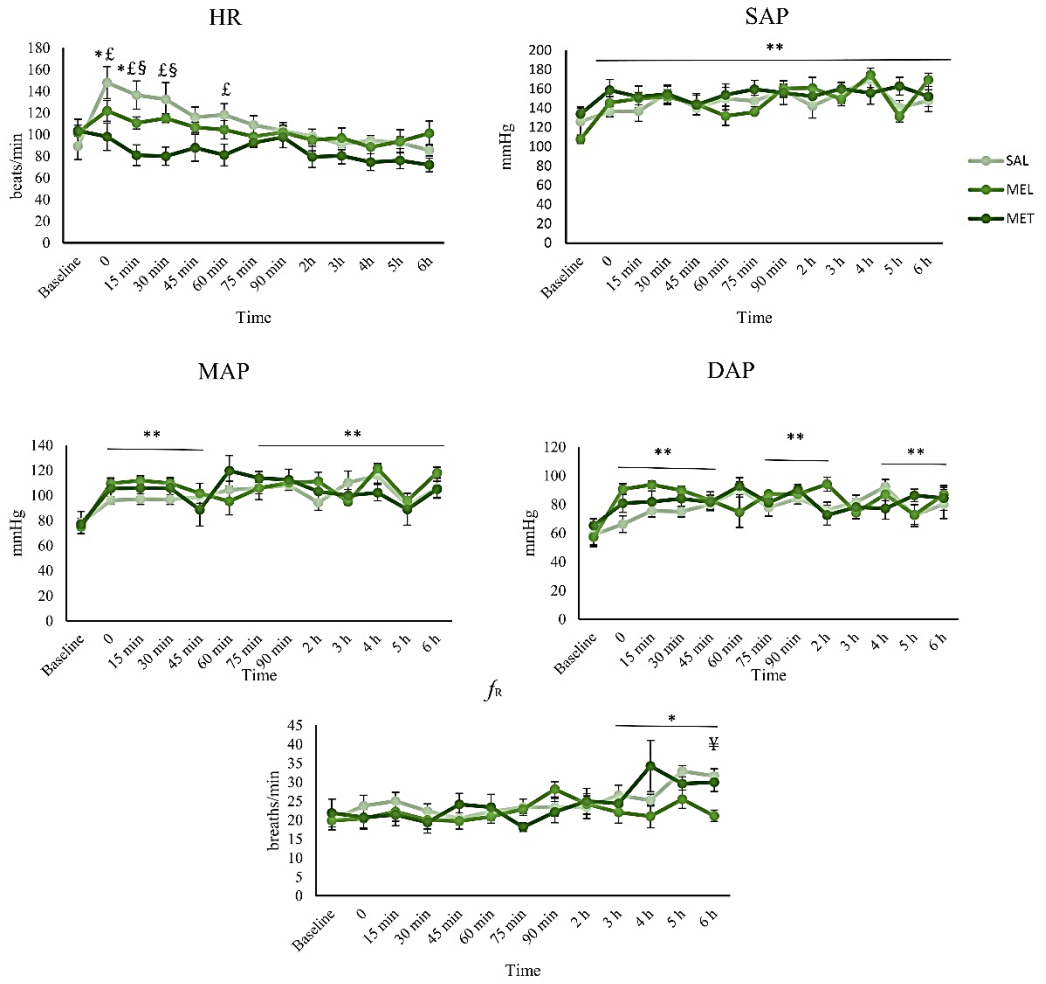

Figure 1. Mean ± standard error of physiologic parameters [heart rate (HR), Systolic, diastolic, and mean arterial blood pressure (SAP, DAP, and MAP), and respiratory rate (f_R)] at baseline, and 15, 30, 45, 60, 75, 90 minutes, and hourly for 6 hours post-surgery in dogs received intravenous saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8) immediately after ovariohysterectomy. * Significant difference from baseline in the SAL, ** Significant difference from baseline in the MEL, £ Significant difference between SAL vs. MET, §Significant difference between MEL vs. MET, ¥ Significant difference between MEL vs. SAL and MET.

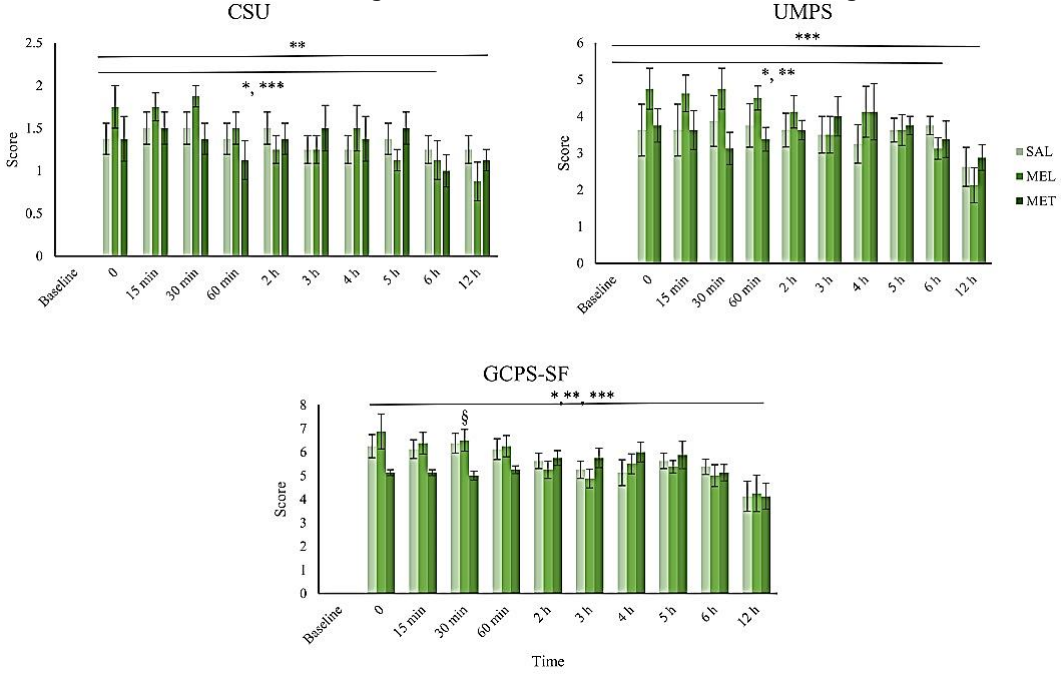

Figure 2. Median ± range (maximum-minimum) of pain scores of the Colorado State University Canine Acute Pain Scale (CSU-UAPS), the University of Melbourne Pain Scale (UMPS), and the Glasgow Composite Pain Scale-Short Form (GCPS-SF) at 0, 15, 30, 60 minutes, and 2, 3, 4, and 6 hours postoperatively in dogs received intravenous saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8) immediately after ovariohysterectomy. * Significant difference from baseline in the SAL, ** Significant difference from baseline in the MEL, *** Significant difference from baseline in the MEL, §Significant difference between MEL vs. MET.

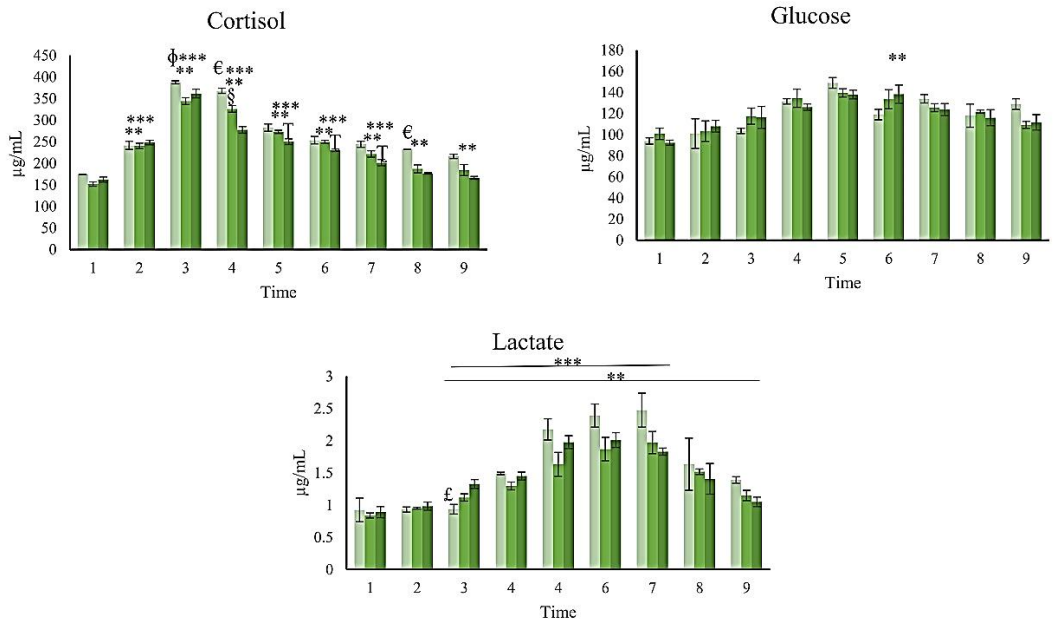

Figure 3. Mean ± standard error of the levels of cortisol, glucose and lactate before anesthesia, and at 30, 60 minutes, and then at 2, 3, 4, 5, 6, 12, and 24 hours post-anesthesia in dogs received intravenous saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8) immediately after ovariohysterectomy. ** Significant difference from baseline in the MEL, *** Significant difference from baseline in the MET, £ Significant difference between SAL vs. MET, § Significant difference between MEL vs. MET, € Significant difference between SAL vs. MEL and MET, ϕ Significant difference between SAL vs. MEL, Ţ Significant difference between MET vs. SAL and MEL.

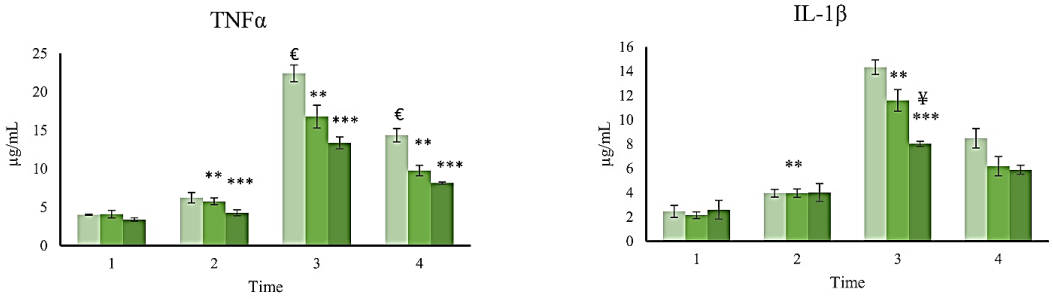

Figure 4. Mean ± standard error of the levels of tumor necrosis factor-alpha (TNFα) and interleukin-1 beta (IL-1β), at 1 hour before anesthesia and 4, 12, and 24 hours post-anesthesia in dogs received intravenous saline (SAL, n = 8), meloxicam (MEL, 0.2 mg/kg, n = 8), or methadone (MET, 0.2 mg/kg, n = 8) immediately after ovariohysterectomy. ** Significant difference from baseline in the MEL, *** Significant difference from baseline in the MET, ¥ Significant difference between MEL vs. SAL and MET, € Significant difference between SAL vs. MEL and MET.

Discussion

In the current study, a trend toward reduced need for rescue analgesia was observed in the methadone group, with only 25% of dogs requiring additional morphine doses post-surgery, compared to 75% in the SAL. The Meloxicam group showed an intermediate requirement for rescue analgesia (50%), with no significant difference compared to either the SAL or MET groups.

The statistically significant within-group differences observed in the CSU-UAPS, UMPS, and GCPS-SF over time are consistent with the established understanding of postoperative pain dynamics in veterinary medicine.[16,17] Surgical trauma initiates an inflammatory cascade and nociceptive signaling, leading to an acute pain response that typically peaks shortly after surgery and gradually subsides as healing progresses and analgesic interventions take effect.[18] This temporal pattern, observed across all groups, including the placebo group, underscores the dynamic nature of postoperative pain and the importance of continuous pain assessment in a clinical setting.

Between-group differences were noted for GCPS-SF at 30 minutes, with group MET showing lower pain scores than group MEL and SAL; however, this was not significant for the SAL. The finding that the SAL group had higher GCPS-SF scores than the MET group, although not statistically significant, most likely due to the small sample size, at 30 minutes post-surgery, is consistent with pharmacological expectations. Methadone, as a potent opioid, would be expected to provide rapid and effective analgesia, thereby significantly reducing pain behaviors and physiological indicators of pain shortly after administration.[19] In contrast, the SAL group, receiving no active analgesic, would experience the full impact of surgical pain, leading to higher pain scores. This

result underscores the immediate and significant analgesic efficacy of methadone in the very early postoperative period, highlighting its importance in preemptive or multimodal pain management strategies for surgical procedures like OHE.[20] Numerous studies validate the effectiveness of methadone in reducing postoperative pain in dogs, often demonstrating its superiority over placebo or less potent analgesics.[19,20]

The finding that group MEL had higher GCPS-SF scores than the MET at 30 minutes after surgery suggests that methadone provided superior early postoperative analgesia compared to meloxicam. This result is generally consistent with the pharmacological profiles of these drugs. Opioids like methadone are known for their rapid onset and potent analgesic effects, making them highly effective for acute, severe pain.[21] NSAIDs, while excellent for inflammatory pain, may have a slower onset of action or be less effective in controlling the initial surge of nociceptive pain immediately after surgery.[12] Several studies comparing NSAIDs and opioids in canine surgery have shown that opioids often provide more robust analgesia in the immediate postoperative period.[22,23]

Meloxicam primarily provides analgesia by inhibiting prostaglandin synthesis at the site of inflammation.[9] In contrast, methadone acts centrally on opioid receptors to modulate pain perception.[19] The superior pain control offered by methadone in the early postoperative phase compared to meloxicam suggests that for the acute, intense pain associated with OHE, central analgesia provided by opioids may be more effective or have a faster onset of action in mitigating the initial pain surge. This aligns with the understanding that opioid analgesics are often considered the cornerstone for managing moderate to severe acute postoperative pain due to their potent analgesic effects.[21] The higher pain scores in the meloxicam group at this early point could indicate that the anti-inflammatory effects of meloxicam had not yet fully manifested or were insufficient to control the acute nociceptive pain as effectively as methadone. However, some studies suggest that meloxicam alone can provide adequate postoperative analgesia in canine OHE, particularly when administered pre-emptively.[24,25] The discrepancy might lie in the specific timing of assessment and the intensity of the surgical stimulus.

In contrast to GCPS-SF, no significant differences were identified for the CSU-UAPS or the UMPS across groups. The GCPS-SF is a validated, multidimensional pain assessment tool that incorporates both behavioral and physiological parameters to provide a more objective measure of dog pain.[26] The CSU-UAPS and UMPS are also validated pain assessment tools that rely on behavioral observations and physiological parameters. The lack of significant differences between groups for these scales could be attributed to several factors. It is possible that these scales may have had less sensitivity in detecting subtle between-group differences in analgesic efficacy, especially if the overall pain levels were moderate or if the scales were not optimally suited for the specific nuances of pain expression in the study population. Alternatively, it could suggest that beyond the very early postoperative period (30 minutes for GCPS-SF), the analgesic effects of meloxicam and methadone, or the natural resolution of pain, converged to a point where these scales no longer detected statistically significant differences between the treatment groups. This highlights the importance of using multiple pain assessment tools and considering their individual sensitivities and specific time points of assessment when evaluating analgesic efficacy.[27] This finding is not entirely unprecedented in the literature, as different pain scales can have varying sensitivities and specificities, and their ability to detect subtle differences between analgesic regimens can depend on the intensity of pain, the timing of assessment, and the specific behaviors or physiological parameters they emphasize.[17,27,28] This underscores the importance of employing a battery of pain assessment tools to capture a comprehensive picture of pain and analgesic efficacy, as different scales may reveal different aspects of the pain experience.

The observed significant effect of time on HR postoperatively highlights the dynamic physiological changes that occur post-surgically. The MET group consistently exhibited the lowest HR in the postoperative phase compared to both saline and meloxicam. It has been shown that opioids, such as methadone, induce bradycardia through their vagomimetic effects.[19,21] Additionally, in group MEL, HR tended to be higher compared to group MET. Meloxicam is generally not anticipated to depress cardiorespiratory function at therapeutic dosages significantly,[12] which aligns with its relatively higher HR compared to methadone. The higher values of HR in the SAL postoperatively are consistent with the conventional expectations, where pain-induced sympathetic activation might lead to an elevated HR.

The fluctuating blood pressure observations suggest that while the analgesic protocols may exert acute, transient effects on blood pressure, their overall impact on blood pressure might not be profoundly different or sustained over a longer period. The lower blood pressure observed in the MET group aligns with the known vasodilatory and hypotensive effects of opioids.[21] Conversely, the higher blood pressure in the SAL group could reflect a pain-induced sympathetic response in the absence of adequate analgesia. Existing literature on meloxicam typically indicates minimal impact on blood pressure at therapeutic doses .[12] Studies comparing various analgesic protocols often report diverse effects on blood pressure, which can be influenced by the specific

drugs, dosages, and surgical procedures.[29]

f_R was significantly lower in the MET at 6 hours post-surgery, which is consistent with the known respiratory depressant effects of opioids, which can manifest as reduced respiratory rate or shallow breathing.[21] This delayed effect could be attributed to the sustained action of methadone or a cumulative effect over time. In contrast, meloxicam, as an NSAID, is not typically associated with direct respiratory depression.[12] These findings highlight the differential impact of the administered analgesics on respiratory function, emphasizing the importance of monitoring respiratory parameters, particularly in patients receiving opioid analgesia, even several hours post-surgery.

Cortisol levels demonstrated significant impacts of time, group, and interaction, consistent with the understanding that surgical stress profoundly activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased cortisol secretion.[30] A particularly striking finding was the consistently higher cortisol levels in group MEL compared to both groups SAL and MET across several time points. This observation suggests that while meloxicam provides adequate analgesia, its capacity to mitigate the overall neuroendocrine stress response may be less pronounced than that of methadone. Opioids are well-documented for their ability to attenuate the surgical stress response and reduce cortisol release through their central nervous system effects and direct modulation of the HPA axis.[18,19] Therefore, the lower cortisol levels in the methadone group are in concordance with established pharmacological principles. Both lactate and glucose levels were significantly affected by time, a physiological response expected to meet the metabolic demands and stress induced by surgical trauma. Surgical stress typically leads to a catabolic state, characterized by hyperglycemia resulting from increased catecholamine and cortisol release, which promotes gluconeogenesis and glycogenolysis.[31,32] Elevated lactate levels can also occur due to increased anaerobic metabolism in response to tissue hypoperfusion or heightened metabolic demand during stress. Opioids can influence glucose metabolism, and their analgesic effects can indirectly reduce stress-induced metabolic alterations.[19] Existing literature consistently demonstrates that surgical procedures like OHE can induce changes in glucose and lactate levels in dogs.[31,33]

The observed significant influence of time, group, and time and group interaction on TNFα levels is consistent with the well-established understanding that surgical procedures, including OHE, induce a systemic inflammatory response .[31,34] The TNFα levels in the SAL group exhibited significantly higher levels compared to those in the MEL and MET groups at specific time points. Meloxicam primarily exerts its effects by inhibiting cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis and subsequent inflammation.[12] While NSAIDs are generally expected to attenuate inflammatory responses, the elevated TNFα in the meloxicam group suggests a nuanced modulation of the inflammatory cascade. This suggests that meloxicam, despite its analgesic efficacy, may not completely suppress all pro-inflammatory pathways, potentially leading to a compensatory upregulation of other cytokines, such as TNFα. Alternatively, it might indicate that the systemic inflammatory response was not mitigated to the same extent as with methadone. Opioids, including Methadone, are known to possess immunomodulatory properties that can influence cytokine production.[21] The lower TNFα levels observed in the methadone group could be attributed to these immunomodulatory effects, which may extend beyond simple pain relief to directly influence inflammatory mediator release. Similarly, IL-1β levels were significantly affected by time, as well as the interaction between time and group, with a notable difference at time 3 between the groups SAL vs. MEL and MET. IL-1β is a pivotal pro-inflammatory cytokine that orchestrates the initiation and amplification of the inflammatory response .[31] Its elevation post-surgery is a predictable physiological consequence of tissue trauma. Lower levels of IL-1β in group MEL and MET align with the expectation that meloxicam and methadone, through their respective anti-inflammatory or immunomodulatory actions, effectively attenuated the IL-1β response compared to saline.

In conclusion, methadone-treated dogs consistently exhibited reduced need for rescue analgesia and lower heart rates, offering superior pain control and contributing to better cardiorespiratory stability. While meloxicam also showed some beneficial effects, particularly in modulating inflammatory markers, its impact on pain scores and cardiorespiratory stability was less pronounced than that of methadone. Our finding emphasizes the importance of multimodal analgesia, where opioids can address the acute nociceptive component and NSAIDs can target the inflammatory component, especially in the recovery phase. Future research could explore the long-term effects of these agents and their combinations in various surgical settings.

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Conflict of Interest

The authors declare no conflict of interest.

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