

## Sprayed Intraperitoneal and Incisional Lidocaine Reduces Early Postoperative Pain After Ovariohysterectomy in Dogs

Ender ÇOLAK<sup>1</sup> Oktay YILMAZ<sup>2\*</sup>

<sup>1</sup>Muğla Metropolitan Municipality, Department of Agricultural Service, 48000, Muğla, Turkey

<sup>2</sup>Afyon Kocatepe University, Faculty of Veterinary Medicine, Department of Obstetrics and Gynaecology, 03200, Afyonkarabısar, Turkey

### ABSTRACT

In the present study, it was aimed to investigate the effect of intraperitoneal and incisional sprayed lidocaine on postoperative stress, oxidative stress and pain in dogs undergoing ovariohysterectomy. The control group (n=12) received intraperitoneal and incisional sprayed 0.9 % NaCl, whereas the preparation of lidocaine (8.8 mg/kg) with the equal volume of 0.9 % NaCl following calculation of the individual doses was sprayed in the experiment group (n=12). Modified Melbourne pain assessment was performed before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T<sup>1/2</sup>) and at 1 (T1), 2 (T2), 4 (T4) and 6 (T6) hours after the end of surgery. Venous blood samples were collected to measure the concentrations of serum cortisol, total oxidant status (TOS) and total antioxidant status (TAS) at related times. Oxidative stress index (OSI) was calculated by the determination of the rate of TOS/TAS. The concentrations of cortisol, TAS and OSI did not show any significant difference between groups (p > 0.05). The concentration of TOS was the highest at T1 in the experiment group (p<0.05). The pain scores in the experiment group were lower (p<0.05) than those detected at T2 (p<0.05), T4 (p<0.01) and T6 (p<0.01) in the control group. In conclusion, it was stated that the treatment of intraperitoneal and incisional sprayed lidocaine is effective on postoperative pain management in dogs undergoing ovariohysterectomy.

**Keywords:** Lidocaine, TOS, TAS, OSI, Pain

\*\*\*

### İntraperitoneal ve İnsizyonel Sprey Lidokain Uygulaması Köpeklerde Ovaryohistektomi Sonrası Erken Postoperatif Ağrını Azaltır

### ÖZ

Sunulan çalışmada, ovariohistektomi yapılan köpeklerde intraperitoneal ve insizyonel sprey lidokain uygulamasının operasyon sonrası stres, oksidatif stres ve ağrı üzerine etkilerinin araştırılması amaçlandı. Kontrol grubuna (n=12) sprey şeklinde intraperitoneal ve insizyonel % 0.9 NaCl uygulanırken, deneme grubu (n=12) bireysel doz hesaplamasını takiben eşit dozda % 0.9 NaCl ile hazırlanmış lidokain (8,8 mg/kg) aldı. Modifiye Melbourne ağrı skorlaması sedasyon öncesi (T), operasyon bitimi (T0), operasyondan 30 dakika (T<sup>1/2</sup>), 1 (T1), 2 (T2), 4 (T4) ve 6 (T6) saat sonra gerçekleştirildi. İlgili zamanlarda venöz kan örnekleri alınarak, serum kortizol, total oksidan durum (TOD) ve total antioksidan durum (TAD) ölçümleri yapıldı. Oksidatif stres indeksi (OSI) TOD/TAD oranına göre belirlendi. Kortizol, TAD ve OSI değerlerinin gruplar arasında istatistiksel olarak fark oluşturmadığı belirlendi (p > 0.05). Deneme grubunda TOD düzeyinin T1 zamanında en yüksek seviyede olduğu gözlemlendi (p<0.05). Deneme grubundaki ağrı skorlarının kontrol grubundaki T2 (p<0.05), T4 (p<0.01) ve T6 (p<0.01) zamanlarına göre daha düşük olduğu tespit edildi. Sonuç olarak, ovariohistektomi yapılan köpeklerde intraperitoneal ve insizyonel sprey lidokain uygulamasının postoperatif ağrı yönetiminde etkili olduğu ifade edilmektedir.

**Anahtar Kelimeler:** Lidokain, TOD, TAD, OSI, Ağrı

To cite this article: Çolak E, Yılmaz O. Sprayed Intraperitoneal and Incisional Lidocaine Reduces Early Postoperative Pain After Ovariohysterectomy in Dogs. Kocatepe Vet J. (2020) 13(4)396-405

Submission: 25.09.2020 Accepted: 18.11.2020 Published Online: 23.11.2020

ORCID ID; EÇ: 0000-0003-0260-1590, OY: 0000-0002-9722-5155

\*Corresponding author e-mail: oktayyilmaz@aku.edu.tr

## INTRODUCTION

Ovariohysterectomy is a common surgical procedure in female dogs (Gunay et al. 2011, Yilmaz et al. 2014, Kibar et al. 2019, Korkmaz et al. 2019) due to its potential benefits, including the prevention of unwanted pregnancies, mammary tumour formation, pyometra and the presence of vaginal discharge due to pyometra (Davidson et al. 2004). Internationally, veterinary canine ovariohysterectomies are performed under routine surgical protocols and in controlled environments that produce relatively comparable amounts of stress and tissue injury. Apart from the use of analgesics, medical intervention is generally limited (Gautier et al. 2019). The wide spectrum of unfavorable alterations in normal body homeostasis following surgery is collectively referred to as surgical stress (Anup et al. 1999, 2000). The major source of stress for the animal is not only the surgery procedure itself, but also surgery-associated parameters such as human handling, anesthesia-induced dysphoria, pain, analgesia and mid or long term care in a hospitalization unit (Nenadovic et al. 2017). Moreover, it has been demonstrated that oxidative stress is another unexpected postoperative condition of ovariohysterectomy (Lee and Kim 2014). Cumulatively, tissue damage, oxidative stress and pain during and after surgery may lead to poor postoperative outcomes (Sies 1997).

It has been reported that ovariohysterectomies on dogs are generally performed without specific treatment for pain by practitioners (Carpenter et al. 2004). The reasons for this approach include the expense of analgesics, the data recording requirements of those analgesic drugs, concerns that the recovery process might be impaired (Lamont et al. 2000, Carpenter et al. 2004) and the difficulties in pain recognition (Carpenter et al. 2004). Local anesthetics have been widely used in the veterinary field due to its analgesia potency by regional blockade, easy accessible property and comparatively inexpensive price. Lidocaine is considered a good option as a local analgesic due to its extended time of activity (Wilson et al. 2004). The anesthetic and analgesic effects and postoperative pain relief of various treatment methods of lidocaine have previously been reported, including line block (McKune et al. 2014), local infiltration to mesovarium (Bubalo et al. 2008), intravenous (Tsai et al. 2013, Lu et al. 2016), intraperitoneal (Kibar et al. 2019, Carpenter 2004) and incisional (Carpenter 2004). However, the data of sprayed intraperitoneal and incisional lidocaine treatment under the combination of xylazine and ketamine anesthesia are limited. Therefore, the present study was aimed to demonstrate the effect of sprayed intraperitoneal and incisional lidocaine treatment on the management of postoperative pain and oxidative stress in dogs undergoing ovariohysterectomy.

## MATERIALS and METHODS

A total of 24 bitches of various breeds referred to the university animal hospital for elective ovariohysterectomy were used in the study. Animals weighing  $26 \pm 1.2$  kg were randomly separated in two groups. All procedures were approved by the Local Ethic Committee of Afyon Kocatepe University (AKUHADYK-159-17). All animals were kept at the hospitalization unit of the animal hospital and food or water consumption was not allowed for the eight hours immediately before ovariohysterectomy.

### Anesthesia and Surgery Protocol

Sedation was performed by 0.045 mg/kg subcutaneous (s.c.) atropine (Atropin, Vetaş, Turkey) 30 minutes (min) prior to the injection of xylazine HCl (2-3 mg/kg intramuscular (i.m.); Alfazyne 2%, Egevet, Turkey). Meloxicam (0.2 mg/kg, s.c., Maxicam, Sanovel, Turkey) was injected following the sedation. Induction of anesthesia was continued by 10 mg/kg i.m. ketamine HCl (Alfamyl 2%, Egevet, Turkey). An intravenous (IV) catheter was introduced into the cephalic vein for further blood sampling and fluid therapy. Intravenous lactated Ringer's solution (10 mL/kg/h) was provided throughout the procedure. All surgeries were performed by the same surgeon from median line in a routine manner to avoid bias between the groups as previously described elsewhere (Korkmaz et al. 2019). Briefly, the ventral abdomen was prepared aseptically for ovariohysterectomy and a midline incision (1.5 - 2.5 cm) was performed. The uterine ligament was held by a uterine hook following the incision of line alba to reach the abdominal cavity. The cranial part of both ovaries and cervix uteri were ligatured. In the experiment group (n=12), lidocaine (8.8 mg/kg, L-anest 2%, Alke, Turkey) was prepared using the equal volume of saline following calculation of the individual doses. During each step of removing the ovaries and the entire uterus, lidocaine was sprayed to the related parts as well as the left and right or cranial and caudal parts of the abdominal cavity and finally, to the incision line just before closing the skin. The control group received only sprayed saline. The durations of anaesthesia and surgery were recorded. The animals were observed for signs of lidocaine toxicity during the postoperative process. Postoperative care was maintained by daily injections of penicillin + streptomycin (20 mg/kg, i.m. Penoksal, Vilsan, Turkey) for five consecutive days. Sutures were removed ten days after surgery.

### Assessment of concentrations of blood cortisol, total oxidant status, total antioxidant status and oxidative stress index

Blood samples were collected following the each pain assessment process. Blood samples were immediately centrifuged at 5000 rpm for 10 minutes and then sera were stored at  $-20^{\circ}\text{C}$  until further analysis of the

concentrations of cortisol, total oxidant status (TOS) and total antioxidant status (TAS). The analysis of TOS and TAS (Erel 2004, Erel 2005) before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T<sup>1/2</sup>) and at 1 (T1), 2 (T2) and 4 (T4) hours after the end of surgery and as well as the cortisol at T, T0, T<sup>1/2</sup>, T1, T2, T4 and T6 was performed by commercial kits using ELISA method (Table 1). Oxidative stress index (OSI) was determined by division of the values of TOS ( $\mu\text{mol H}_2\text{O}_2 \text{ Eq/L}$ ) to TAS ( $\text{mmol Trolox Eq/L}$ ) (Baysal et al. 2012).

### Assessment of pain scoring

Modified Melbourne Pain Scale (MMPS) was used for the evaluation of pain by the same person, who did not know the groups in the study (Table 2). This blind assessment was performed at T, T0, T<sup>1/2</sup>, T1, T2, T4 and T6. Butorphanol (0.2 mg/kg, i.v.,

Butomidol, Richter Pharma A.G. Wels, Austria) was prepared as a rescue analgesic at any time, when the MMPS was scored higher than 9 points.

### Statistics

The distribution of normality of data was analysed by Shapiro-Wilk normality test. It was found that all data had the normal distribution. Therefore, differences in duration of surgery, pain scores and the concentrations of cortisol, TOS and TAS as well as OSI rates detected during measurement times between the groups were compared by using t test. A repeated measures two way ANOVA test was used to compare differences within the groups (SPSS 16.0). Values were described by mean  $\pm$  Standard Error Mean (SEM). The data were considered to be significantly different at  $p < 0.05$ .

**Table 1:** The information of sensitivity, coefficient of variations and provider of commercial test kits for the measurement of cortisol, total oxidant status (TOS) and total antioxidant status (TAS).

Test	Sensitivity	Coefficient of variations		Provider
		Intraassay	Interassay	
Cortisol	2.5 ng/ml	8.1 %	6.6 %	EIA-1887, DRG, USA
TAS	4 $\mu\text{mol/L}$	3.3 %	2.8 %	Mega Tip, Gaziantep, Turkey
TOS	1.20 mmol/L	3.9 %	3.2 %	Mega Tip, Gaziantep, Turkey

**Table 2:** Modified Melbourne Pain Scoring Scale

Dog Name/ID: _____ Date: _____ Time Point: _____ Breed: _____	
Total UMPS Score: _____	
Category and descriptor Score _____	
<i>From outside the cage</i>	
Vocalization (choose only one)*	
Not vocalizing	0
Slight vocalization but dysphoric	1
Intermittent vocalization	2
Continuous vocalization	3
<i>Posture</i>	
a) Guarding or protecting affected area	2
b) Position (choose only one)	
Lateral recumbency	0
Sternal recumbency	1
Sitting, standing, or comfortable	1
Standing with head hanging	2
Moving	1
Abnormal posture and/or uncomfortable, continuous position change	2
<i>Activity (choose one)</i>	
At rest	
Sleeping	0
Semi-conscious	0
Awake	1

Eating	0
Restless (pacing continuously; getting up and down)	2
Rolling and thrashing	3
<hr/>	
<i>From inside the cage</i>	
Mental status (choose only one)** Baseline minus current score = overall score	
Too sedate to evaluate or dysphoric	0
Submissive	1
Uninterested in people (unusual for this dog)	2
Overtly friendly	3
Wary or Aggressive	4
<hr/>	
<i>Response to palpation (choose only one)***</i>	
Normal, allows palpation of surgical site	0
Allows but then moves away, tenses or looks when surgical area touched	1
Increased whining or painful expression when surgical area touched	2
Will not allow general surgical area to be touched	3
<hr/>	
<i>Vocalization (choose only one)*</i>	
Not vocalizing	0
Vocalizing but responds to quiet voice and/or stroking	1
Vocalizing when touched	2
Intermittent vocalization	2
Continuous vocalization	3

The minimum possible score is 0; the maximum possible score is 20.\*Does not include alert barking. \*\*For this category, score recorded is the score obtained after surgery minus the score obtained before surgery. \*\*\*Palpate around the general surgical area starting at the dorsal end and working toward incision site

## RESULTS

Duration of ovariohysterectomy in the control group was  $25.50 \pm 3.50$  minutes, whereas it was  $26.30 \pm 3.35$  minutes in the experiment group. It was found that the duration of surgery did not differ significantly between groups. It was observed that the concentrations of cortisol in the control group slightly increased until T2 and decreased after T4. However, these changes were not significant statistically ( $p > 0.05$ ). A similar pattern was also observed in the experiment group but only the concentrations detected at T1 and T2 were higher ( $p < 0.001$ ) than those obtained at T (Table 3). Although lower concentrations of cortisol were detected at T4 and T6 in the experiment group as compared to the control group, the differences at other measurement times between the control and the experiment groups were not significant statistically ( $p > 0.05$ ) (Figure 1).

It was seen that the concentration of TOS detected at T slightly increased at subsequent measurement times in the control group but all those changes were not significant statistically ( $p > 0.05$ ) (Table 4). The concentrations of TOS detected in the experiment group showed that the highest concentration of TOS was at T1 ( $p < 0.05$ ) and this was statistically similar to

the other measurement times, except T. In addition, the TOS value at T1 in the experiment group was higher ( $p < 0.05$ ) than those detected in the control group. On the other hand, the concentrations of TAS did not show any significant difference within or between the groups ( $p > 0.05$ ) (Table 5).

The OSI value in the control group increased at the end of surgery and was higher at other measurement times than those detected at the sedation time, but those changes were not statistically significant ( $p > 0.05$ ). Similarly, non-significant higher values at T1 and T4 in the experiment group were observed. Moreover, there was no significant difference between groups ( $p > 0.05$ ) (Table 6).

The scores of pain assessment initiated at the end of surgery in the control and the experiment groups are shown in Table 7. Accordingly, it was observed that the pain scores gradually increased until T4 ( $p < 0.001$ ) and remained high in the control group, whereas the pain scores in the experiment group increased ( $p < 0.001$ ) until T1 and remained high (Table 7). However, the comparison of pain scores between control and experiment groups revealed that pain scores obtained at T2 ( $p < 0.05$ ), T4 ( $p < 0.01$ ) and T6 ( $p < 0.01$ ) in the control group were higher than those detected in the experiment group (Figure 2).

**Table 3:** The concentrations of cortisol (ng/dL) detected before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T ½) and at 1 (T1), 2 (T2), 4 (T4) and 6 (T6) hours after the end of surgery following the pain assessment process (Mean±SEM).

Blood Sampling Time (hour)	Control (n=12)	Experiment (n=12)
T	136.45 ± 21.19	100.34 ± 12.36 <sup>b</sup>
T 0	184.96 ± 24.28	187.44 ± 26.73 <sup>ab</sup>
T ½	196.69 ± 29.62	206.98 ± 38.77 <sup>ab</sup>
T 1	212.36 ± 31.23	223.80 ± 24.98 <sup>a</sup>
T 2	241.45 ± 33.48	266.77 ± 27.18 <sup>a</sup>
T 4	239.64 ± 24.74	200.32 ± 22.36 <sup>ab</sup>
T 6	211.12 ± 28.41	158.62 ± 20.71 <sup>ab</sup>

Small <sup>(ab)</sup> letters in superscript indicate significant differences (p<0.001) within the experiment group.

**Table 4:** The concentrations of total oxidant status (TOS) (µmol/L) detected before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T ½) and at 1 (T1), 2 (T2) and 4 (T4) hours after the end of surgery following the pain assessment process (Mean±SEM).

Blood Sampling Time (hour)	Control (n=12)	Experiment (n=12)
T	2.65 ± 0.21	2.72 ± 0.37 <sup>b</sup>
T 0	3.77 ± 0.51	4.47 ± 0.72 <sup>ab</sup>
T ½	3.63 ± 0.68	3.54 ± 0.16 <sup>ab</sup>
T 1 *	3.13 ± 0.41	4.93 ± 0.61 <sup>a</sup>
T 2	3.44 ± 0.43	3.42 ± 0.34 <sup>ab</sup>
T 4	3.82 ± 0.69	4.73 ± 0.58 <sup>ab</sup>

Small <sup>(ab)</sup> letters in superscript indicate significant differences (p<0.05) within the experiment group. \* indicates significant difference (p<0.05) between control and experiment groups.

**Table 5:** The concentrations of total antioxidant status (TAS) (mmol/L) detected before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T ½) and at 1 (T1), 2 (T2), and 4 (T4) hours after the end of surgery following the pain assessment process (Mean±SEM).

Blood Sampling Time (hour)	Control (n=12)	Experiment (n=12)
T	1.84 ± 0.06	1.83 ± 0.15
T 0	1.80 ± 0.09	1.85 ± 0.01
T ½	1.85 ± 0.09	1.86 ± 0.02
T 1	1.96 ± 0.23	1.78 ± 0.07
T 2	1.84 ± 0.01	1.86 ± 0.01
T 4	1.72 ± 0.10	1.80 ± 0.10

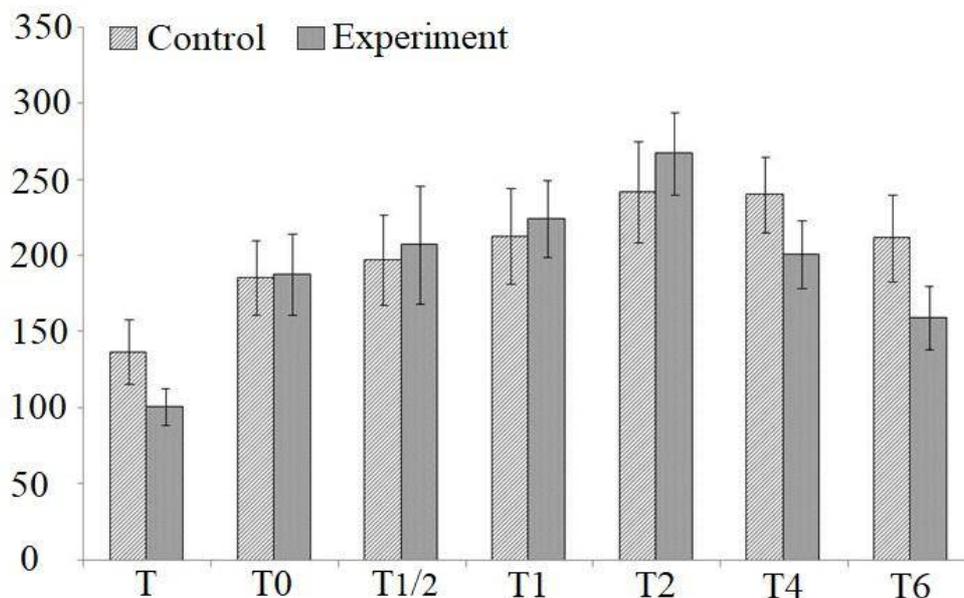
**Table 6:** The oxidative stress index (OSI) [TOS (µmol H<sub>2</sub>O<sub>2</sub> Eq/L)/TAS (mmol Trolox Eq/L)] detected before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T ½) and at 1 (T1), 2 (T2), and 4 (T4) hours after the end of surgery following the pain assessment process (Mean±SEM).

Blood Sampling Time (hour)	Control (n=12)	Experiment (n=12)
T	1.74 ± 0.13	1.84 ± 0.44
T 0	2.09 ± 0.24	2.41 ± 0.39
T ½	1.88 ± 0.36	1.89 ± 0.09
T 1	1.76 ± 0.38	2.80 ± 0.36
T 2	1.87 ± 0.24	1.83 ± 0.18
T 4	2.27 ± 0.42	2.65 ± 0.28

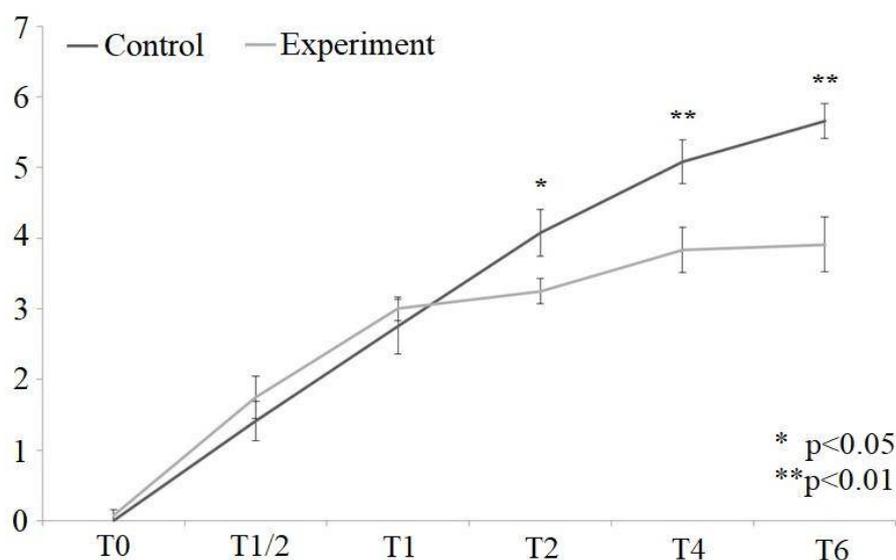
**Table 7:** Distribution of pain scores (Mean±SEM) detected before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T 1/2) and at 1 (T1), 2 (T2), 4 (T4) and 6 (T6) hours after the end of surgery in the control and experiment groups.

Pain Scoring Time (hour)	Control (n=12)	Experiment (n=12)
T 0	0.00 ± 0.00 <sup>c</sup>	0.08 ± 0.08 <sup>c</sup>
T 1/2	1.41 ± 0.28 <sup>d</sup>	1.75 ± 0.30 <sup>b</sup>
T 1	2.75 ± 0.39 <sup>c</sup>	3.00 ± 0.17 <sup>a</sup>
T 2	4.08 ± 0.33 <sup>b</sup>	3.25 ± 0.18 <sup>a</sup>
T 4	5.08 ± 0.31 <sup>ab</sup>	3.83 ± 0.32 <sup>a</sup>
T 6	5.66 ± 0.25 <sup>a</sup>	3.91 ± 0.39 <sup>a</sup>

Small <sup>(abc)</sup> letters in superscript indicate significant differences (p<0.001).



**Figure 1.** Representative changes of concentrations of cortisol (ng/dL) before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T 1/2) and at 1 (T1), 2 (T2), 4 (T4) and 6 (T6) hours after the end of surgery between the control and experiment groups.



**Figure 2.** The comparison of pain scores detected before sedation (T), at the end of surgery (T0), 30 minutes after surgery (T 1/2) and at 1 (T1), 2 (T2), 4 (T4) and 6 (T6) hours after the end of surgery between control and experiment groups.

## DISCUSSION

Ovariohysterectomy is a common elective surgery in which tissue trauma and inflammation due to surgical manipulations cause pain in dogs (Lemke et al. 2002). It has been reported that the postoperative pain following 24 hours changes animal behaviours (Lemke et al. 2002; Tsai et al. 2013). It has been postulated that ovariohysterectomy is also a common model for the evaluation of postoperative pain and efficacy of analgesic drugs, since the surgery is performed in healthy dogs without the evidence of pain (Devitt et al. 2005, Michelsen et al. 2012, Tsai et al. 2013, Yilmaz et al. 2014, Korkmaz et al. 2019). Therefore, the effect of intraperitoneal and incisional administration of lidocaine on postoperative pain was evaluated in dogs undergoing ovariohysterectomy in this study.

It has been reported that standard ovariohysterectomy takes  $18.3 \pm 3.9$  minutes, while  $20.8 \pm 4$  minutes is needed for laparoscopic ovariohysterectomy (Devitt et al. 2005). In another report, it has been stated that ovariohysterectomies are performed by experienced veterinary surgeons in 13 to 28 minutes (Michelsen et al. 2012). In the present study, ovariohysterectomies were performed in  $25.50 \pm 3.50$  minutes and  $26.30 \pm 3.35$  minutes in the control and the experiment groups, respectively. The duration of surgery between groups did not show any significant difference and these durations in both groups were consistent with above-mentioned reports (Devitt et al. 2005, Michelsen et al. 2012).

Local anesthetics such as lidocaine have been widely used in the veterinary field however, lidocaine disparately from other analgesic drugs, completely blocks the sensory nerve fibres and inhibits the development of pain by preventing central sensitization (Lemke and Dawson 2000). The pharmacokinetics of lidocaine 2 % with the combination of epinephrine (1:200.000-1:400.000) have been showed that plasma concentrations rapidly decrease with no toxic concentrations (Wilson et al. 2004). The high volume of local anaesthetics needed for intraperitoneal anesthesia has been observed to cause side effects such as sedation, vomiting, tremors and seizures in a dose dependent manner (Carpenter et al. 2004, Kim et al. 2012). In the present study, it was observed that lidocaine did not cause any of the above-mentioned side effects.

In dogs, major abdominal surgeries such as ovariohysterectomy cause significant hormonal changes in response to surgical manipulation and these changes reach their peak near the end of the surgery or shortly after the recovery from anesthesia. The short-lived stress response to ovariohysterectomy returns to its preoperative values by 5 hours after surgery (Benson et al. 2000) and the concentrations of cortisol returns the baseline value by 12 (Yilmaz et al. 2014) or 24 hours postsurgery (Church et al. 1994, Fox et al. 1994, Benson et al. 2000). Since the

hypothalamus-epiphysis-adrenal axis causes a response during environmental changes, anesthesia and surgery (Church et al. 1994), the serum cortisol concentrations seem to be an important stress marker of this response in bitches. Therefore, serum cortisol concentrations were measured to evaluate the postoperative stress response to surgery in the present study. Furthermore, prostaglandins that are produced under the circumstances of stress (Bugajski et al. 2004, Rettori et al. 2009), stimulate the secretion of corticotrophin releasing hormone (CRH), vasopressin and adrenocorticotrophin hormone (ACTH) (Gadek-Michalska et al. 2005) and the release of corticosterone, by acting directly in the adrenal gland (Wang et al. 2000, Mohn et al. 2005). Therefore, the concentrations of cortisol are indirectly decreased by the inhibition of prostaglandin synthesis via cyclooxygenase (COX) enzyme inhibition (Yilmaz et al. 2014). It is well known that meloxicam has been used in dogs for medium to long term treatment of pain and inflammation and has selectivity against COX2 versus COX1 (Distel et al. 1996, Yilmaz et al. 2014). On the other hand, it has been reported that the concentrations of cortisol rise for 2.5 hours following ovariohysterectomy in meloxicam-injected dogs (Yilmaz et al. 2014). In the present study, it is thought that the acute inhibition of prostaglandin in the control and experiment groups could not be achieved because of the injection of meloxicam during premedication. It has been indicated that the concentrations of cortisol increase at one and two hours after standard or laparoscopic ovariohysterectomy as compared to the basal values (Devitt et al. 2005). Moreover, a rapid decrease in the concentrations of cortisol has been reported following the administration of intraperitoneal local anesthetics during laparoscopic ovariohysterectomy in dogs (Kim et al. 2012). In the present study, similar to previous reports (Devitt et al. 2005, Kim et al. 2012, Yilmaz et al. 2014), increasing postoperative concentrations of cortisol in the control and experiment groups was observed. Although the concentrations of the cortisol measured at T4 and T6 in the experiment group were lower than those detected in the control group, the differences were not statistically significant. It was reported that postoperative concentrations of cortisol increased in ovariohysterectomies performed by unexperienced surgeons (Michelsen et al. 2012). Therefore, it is suggested that the administration of lidocaine is not effective to decrease the postoperative concentrations of cortisol under less traumatic surgery circumstances. Additionally, it is postulated that less traumatic manipulations and more reasonable durations of surgery might be enough to control the concentrations of cortisol.

The trauma caused by the surgical procedure is known to support an oxidative process due to ischaemia or reperfusion (Halliwell 1994). Oxidative stress is a condition which is caused by cellular

destruction following any surgical approach (Sies 1997) and negatively affects the postoperative process (Lee and Kim, 2014). The organism produces antioxidants as a response against oxidative stress to protect the organs (Erel 2004). Since an oxidant-antioxidant balance is involved in the body, lower TOS values would be expected after lidocaine treatment in this study. Nevertheless, in the present study, lidocaine did not decrease the TOS values which were an unexpected result. It has been reported that lidocaine releases the endogenous opioids by inhibition of production of thromboxane A2 via neurokinins (Lauretti 2008) and shows a fast and moderate analgesic effect as compared to other local anesthetics (Hellyer et al. 2007). Furthermore, it has been stated that the infiltration of lidocaine to the mesovarium before ovariohysterectomy may cause hematomas (Bubalo et al. 2008). Additionally, it has been indicated that intramuscular or subcutaneous administration of local anesthetics might cause complications such as dense inflammation, spleen laceration and hernia (Fitzpatrick et al. 2010). Therefore, the cause of higher TOS values in the experiment group may possibly be the inflammation process due to the lidocaine treatment.

In the present study, the concentrations of TAS and OSI values in the control and experiment groups did not show any significant differences. It has been reported that surgery performed in abdominal organs leads to the oxidative stress, especially in erythrocytes for 24 hours (Anup et al. 1999). However, total antioxidant values do not depend on whether the surgery is performed or not (Szymczyk et al. 2003). Although significant difference was observed in TOS values, it is suggested that the treatment of lidocaine is not effective for the management of oxidative stress due to the unchanged TAS and OSI values.

It was observed that the pain scores in the experiment group were lower at T2, T4 and T6, as compared to the control group. This finding was consistent with the previous data (Carpenter et al. 2004, Campagnol et al. 2012), that the lower postoperative pain scores were evident by the administration of intraperitoneal and incisional local anesthetics. Moreover, pain scoring systems are mainly based on the behavioral changes including palpation (Odete and Lesley 2013, Mathews et al. 2014, Epstein et al. 2015). Therefore, it is suggested that local anesthetics may be used for the management of pain level, since the anesthetic agent causes the loss of regional sensation.

It is postulated that surgeries performed at optimal time and less manipulation may be of importance to manage the post-operative stress. Furthermore, it is concluded that the treatment of intraperitoneal and incisional lidocaine is effective on postoperative pain management in dogs undergoing ovariohysterectomy.

## ACKNOWLEDGEMENT

This research article is summarized from the Master of Science thesis entitled with 'Effect of lidocaine on postoperative and oxidative stress and pain in ovariohysterectomized dogs' (Ender Çolak, Thesis No: 2019-009, Institute of Health Sciences, Afyon Kocatepe University).

The authors thank to Prof. Dr. Aziz BULBUL (Mugla Sitki Kocman University) for the technical consultancy of the measurement of cortisol, TOS and TAS.

All procedures were approved by Local Ethic Committee of Afyon Kocatepe University (AKUHADYEK-159-17).

**Conflict of Interest:** The authors declare that they have no conflict of interest.

## REFERENCES

- Anup R, Aparna V, Pulimood A, Balasubramanian KA.** Surgical stress and the small intestine: role of oxygen free radicals. *Surgery*. 1999;125:560-569.
- Anup R, Balasubramanian KA.** Surgical stress and the gastrointestinal tract. *J Surg Res*. 2000; 92:291-300.
- Baysal E, Taysi S, Aksoy N, Uyar M, Celenk F, Karatas ZA, Tarakcioglu M, Bilinç H, Mumbuc S, Kanlikama M.** Serum paraoxonase, arylesterase activity and oxidative status in patients with obstructive sleep apnea syndrome (OSAS). *Europ Rev Med Pharmacol Sci*. 2012; 16:770-774.
- Bubalo V, Moens YP, Holzmann A, Coppens P.** Anaesthetic sparing effect of local anaesthesia of the ovarian pedicle during ovariohysterectomy in dogs. *Vet Anaesth Analg*. 2008; 35:537-542.
- Bugajski J, Gadek-Michalska A, Bugajski AJ.** Nitric oxide and prostaglandin systems in the stimulation of hypothalamic-pituitary-adrenal axis by neurotransmitters and neurohormones. *J Physiol Pharmacol*. 2004;55:679-703.
- Campagnol D, Teixeira-Neto FJ, Monteiro ER, Restitutti F, Minto BW.** Effect of intraperitoneal or incisional bupivacaine on pain and the analgesic requirement after ovariohysterectomy in dogs. *Vet Anaesth Analg*. 2012;39(4):426-430.
- Carpenter RE, Wilson DV, Evans AT.** Evaluation of intraperitoneal and incisional lidocaine or bupivacaine for analgesia following ovariohysterectomy in the dog. *Vet. Anaesthesia and Analg*. 2004;31(1):46-52.
- Church DB, Nicholson AI, Ilkiw JE, Emslie DR.** Effect of non-adrenal illness, anaesthesia and surgery on plasma cortisol concentrations in dogs. *Res Vet Sci*. 1994;56:129-131.
- Davidson EB, Moll HD, Mark EP.** Comparison of laparoscopic ovariohysterectomy and ovariohysterectomy in dogs. *Vet Res*. 2004;33:62-69.

- Devitt CM, Cox RE, Hailey JJ.** Duration, complications, stress, and pain of open ovariohysterectomy versus a simple method of laparoscopic-assisted ovariohysterectomy in dogs. *J Am Vet Med Assoc.* 2005;227(6):921-927.
- Distel M, Mueller C, Bluhmki E, Fries J.** Safety of meloxicam: a global analysis of clinical trials. *Br J Rheumatol.* 1996;35(Suppl 1):68-77.
- Epstein ME, Rodan I, Griffenhagen G, Kadrlik J, Petty M, Robertson SA, Simpson W.** 2015 AAHA/AAFP pain management guidelines for dogs and cats. *J Am Anim Hospital Assoc.* 2015;51(2):67-84.
- Erel O.** A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clin Biochem.* 2004;37:277-285.
- Erel O.** A new automated colorimetric method for measuring total oxidant status. *Clin Biochem.* 2005;38:1103-1111.
- Fitzpatrick CL, Weir HL, Monnet E.** Effects of infiltration of the incision site with bupivacaine on postoperative pain and incisional healing in dogs undergoing ovariohysterectomy. *J Am Vet Med Assoc.* 2010;237:395-401.
- Fox SM, Mellor DJ, Firth EC, Hodge H, Lawoko CRO.** Changes in plasma cortisol concentrations before, during and after analgesia, anaesthesia and anaesthesia plus ovariohysterectomy in bitches. *Res Vet Sci.* 1994;57(1):110-118.
- Gadek-Michalska A, Spyryka J, Bugajski J.** Psychosocial stress affects the involvement of prostaglandins and nitric oxide in the lipopolysaccharide-induced hypothalamic-pituitary-adrenal response. *J Physiol Pharmacol.* 2005;56:287-298.
- Gautier A, Graff EC, Bacek L, Fish EJ, White A, Palmer L, Kuol K.** Effects of ovariohysterectomy and hyperbaric oxygen therapy on systemic inflammation and oxidation in dogs. *Front Vet Sci.* 2019;6:506.
- Gunay A, Gunes N, Gunay U.** Effect of ovariohysterectomy on lipid peroxidation and levels of some antioxidants and biochemical parameters in bitches. *Bull Vet Inst Pulawy.* 2011;55:695-698.
- Halliwell B.** Free radicals and antioxidants: a personal view. *Nutr Rev.* 1994;70:257-265.
- Hellyer PW, Robertson SA, Fails AD.** Pain and Its Management, In: Lumb & Jones' Veterinary Anesthesia and Analgesia, Ed; Tranquilli WJ, Thurmon JC, Grimm KA, 4th Ed., Blackwell Publishing, UK. 2007; pp. 31-60.
- Kibar M, Tuna B, Kısadere İ, Güzelbekteş H.** Comparison of instilled lidocaine and procaine effects on pain relief in dogs undergoing elective ovariohysterectomy. *Israel J Vet Med.* 2019;74(3):148-154.
- Kim YK, Lee SS, Suh EH, Lee L, Lee HC, Lee HJ, Yeon SC.** Sprayed intraperitoneal bupivacaine reduces early postoperative pain behavior and biochemical stress response after laparoscopic ovariohysterectomy in dogs. *Vet J.* 2012;191(2):188-192.
- Korkmaz M, Yilmaz O, Saritas AK, Demirkan I, Jaroszewski JJ.** Evaluation of intraperitoneal and incisional bupivacaine or levobupivacaine for postoperative analgesia in ovariohysterectomized dogs. *Acta Sci Vet.* 2019;47:1666.
- Lamont LA, Tranquilly WJ, Grimm KA.** Physiology of pain. *Vet Clin North Am Small Anim Pract.* 2000;30:703-728.
- Lauretti GR.** Mechanisms of analgesia of intravenous lidocaine. *Rev Bras Anesthesiol.* 2008;58(3):280-286.
- Lee JY, Kim MC.** Comparison of oxidative stress status in dogs undergoing laparoscopic and open ovariectomy. *J Vet Med Sci.* 2014;76(2):273-276.
- Lemke KA, Dawson SD.** Local and regional anesthesia. *Vet Clin North Am Small Anim Pract.* 2000;30:839-857.
- Lemke KA, Runyon CL, Homey BS.** Effects of preoperative administration of ketoprofen on anesthetic requirements and signs of postoperative pain in dogs undergoing elective ovariohysterectomy. *J Am Vet Med Assoc.* 2002;221(9):1268-1275.
- Lu D, Wu C, Yin Y, Ma X.** Analgesic Effects of Lidocaine and Fentanyl Alone or in Combination Undergoing Ovariohysterectomy in Female Dogs. *Pakistan Vet J.* 2016;36(4):435-439.
- Mathews KA, Paley DM, Foster RA, Valliant AE, Young SS.** A comparison of Ketorolac with Flunixin, Butorphanol, and Oxymorphone in controlling postoperative pain in dogs. *Can. Vet J.* 1996;37:557-567.
- McKune CM, Pascoe PJ, Lascelles BDX, Kass PH.** The challenge of evaluating pain and a pre-incisional local anesthetic block. *Peer J.* 2014;2:e341.
- Michelsen J, Heller J, Wills F, Noble G.** Effect of surgeon experience on postoperative plasma cortisol and C-reactive protein concentrations after ovariohysterectomy in the dog: A randomised trial. *Australian Vet J.* 2012;90(12):474-478.
- Mohn CE, Fernandez-Solari J, De Laurentiis A, Prestifilippo JP, de la Cal C, Funk R, Bornstein SR, McCann SM, Rettori V.** The rapid release of corticosterone from the adrenal induced by ACTH is mediated by nitric oxide acting by prostaglandin E2. *Proc Natl Acad Sci USA.* 2005;102:6213-6218.
- Nenadović K, Vučinić M, Radenković-Damjanović B, Janković L, Teodorović R, Voslarova E, Becskei Z.** Cortisol concentration, pain and sedation scale in free roaming dogs treated with carprofen after ovariohysterectomy. *Vet World.* 2017;10(8):888-894.
- Rettori V, Fernandez-Solari J, Mohn C, Zorrilla Zubilete MA, de la Cal C, Prestifilippo JP, De Laurentiis A.** Nitric oxide at the crossroad of immunoneuroendocrine interactions. *Ann NY Acad Sci.* 2009;1153:35-47.
- Sies H.** Oxidative stress: oxidants and antioxidants. *Exp Physiol.* 1997;82:291-295.
- Szymczyk G, Beltowski J, Marciniak A, Kotarski J.** Assessment of serum lipid peroxide levels and antioxidant status in females who had undergone total abdominal hysterectomy without closing of the peritoneum. *Ginekol Pol.* 2003; 74:1397-1403.
- Tsai TY, Chang SK, Chou PY, Yeh LS.** Comparison of postoperative effects between lidocaine infusion, meloxicam, and their combination in dogs undergoing

ovariohysterectomy. *Vet Anaesth Analg.* 2013;40:615-622.

**Wang H, Walker SW, Mason JI, Morley SD, Williams BC.** Role of arachidonic acid metabolism in ACTH-stimulated cortisol secretion by bovine adrenocortical cells. *Endocr Res.* 2000;26:705-709.

**Wilson DV, Barnes KS, Hauptman JG.** Pharmacokinetics of combined intraperitoneal and incisional lidocaine in the dog following ovariohysterectomy. *J Vet Pharmacol Ther.* 2004;27(2):105-109.

**Yilmaz O, Korkmaz M, Jaroszewski JJ, Yazici E, Ulutas E, Saritas ZK.** Comparison of flunixin meglumine and meloxicam influence on postoperative and oxidative stress in ovariohysterectomized bitches. *Polish J Vet Sci.* 2014;17(3):493-499.