

Intraperitoneal administration of lidocaine or tramadol alone or in combination on postoperative pain after ovariohysterectomy in dogs

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Abstract

The present prospective randomized experimental study aimed to assess the intraperitoneal (ip) administration of lidocaine or tramadol, alone or in combination, on postoperative pain management following ovariohysterectomy in dogs. Eighteen healthy female mixed-breed dogs, aged 1–2 years, weighed 16.7 ± 3.8 kg, were used. Animals were sedated with acepromazine (0.1 mg/kg, intramuscular). Forty minutes later, anaesthesia was induced through intravenous titration with diazepam (0.5 mg/kg) and ketamine (10 mg/kg) and maintained with isoflurane 1.5%. Afterwards, ovariohysterectomy was performed, and prior to the closure of the linea alba, animals received lidocaine containing epinephrine (8.8 mg/kg, ip) in group L, tramadol (4 mg/kg, ip) in group T and lidocaine containing epinephrine (8.8 mg/kg, ip) plus tramadol (4 mg/kg, ip) in the LT group. Cortisol, vital signs and pain scoring systems were evaluated at different time points. Vital signs did not change among the groups. Cortisol level in the LT group significantly decreased compared to the L and T groups one, three and six hours after surgery. Pain scores also did not change among the groups based on Sammarco and Simple descriptive (SDS) scoring method. However, pain scores in the LT group were higher than the two other groups according to the University of Melbourne pain scale (UMPS) and the short form of Glasgow pain scale (CMPS-SF). According to the obtained results, the combination of lidocaine and tramadol seemed to be able to provide better analgesia compared with their separate administration. Therefore, combined intraperitoneal administration of lidocaine (8.8 mg/kg) and tramadol (4 mg/kg) with a final volume of (0.2 ml/kg) following ovariohysterectomy is recommended.

KEYWORDS

dog, intraperitoneal, lidocaine, ovariohysterectomy, tramadol

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1 | INTRODUCTION

Ovariohysterectomy is one of the most common surgeries in small animals (Campagnol et al., 2012; Carpenter et al., 2004; Guerrero et al., 2016). Among the upsides of this surgery, mention can be made of population control, prevention of diseases related to the reproductive system and decrease in the unpleasant behaviours associated with sex hormones (Pereira et al., 2018). Ovariohysterectomy is classified as a major surgery (Hardie et al., 1997). Following this surgical procedure, mild to moderate pain occurs (Hardie et al., 1997; Campagnol et al., 2012). Over the recent years, there has been a growing interest in the use of drugs to improve analgesia (Campagnol et al., 2012). Postoperative pain (an acute and pathological pain) leads to many adverse effects, including reduced food intake, increased protein catabolism, impaired respiratory function, irregular heart rhythm, increased central sensitivity to painful stimuli, augmented postoperative stress, suppressed immune system, rise in arterial blood pressure, delayed wound healing, negative protein balance, reduced food intake and maladaptive behaviours such as self-harm. (Gwendolyn & Carrol, 1996; Gaynor, 1999; Flecknell & Watermen-Pearson, 2000). For pain control, topical anaesthetics and opioid analgesics are utilized (Carpenter et al., 2004; Yazbek and Fantoni, 2005; Campagnol et al., 2012; Morgaz et al., 2013). Lambertini et al., 2018; Chilkot et al., 2019). Furthermore, intraperitoneal administration has been employed to control abdominal postoperative pain in human and veterinary medicine. For intraperitoneal administration, a local anaesthetic or analgesic is applied to the surgical site and the viscera before suturing the abdominal wall (Carpenter et al., 2004; Ng et al., 2002; Golubovic et al., 2009; Campagnol et al., 2012; Guerrero et al., 2016; Lambertini et al., 2018; Chilkot et al., 2019). Today, intraperitoneal administration of topical anaesthetics is a valuable and approved method for controlling postoperative pain (Chilkot et al., 2019). Several studies have shown that the intraperitoneal administration of lidocaine or bupivacaine is sufficient for pain control after surgery in dogs (Campagnol et al., 2012; Carpenter et al., 2004; Chilkot et al., 2019; Guerrero et al., 2016; Lambertini et al., 2018). Furthermore, over the recent decades, several clinical studies have reported effective response to the combined use of opioid drugs such as tramadol or morphine and topical anaesthetics, such as bupivacaine, after open or laparoscopic abdominal surgery in humans. The drug combination has been found to result in a longer and deeper pain control in comparison to the separate use of each drug (Ng et al., 2002; Karsli et al., 2003; Memis, 2005; Golubovic et al., 2009). Anaesthetic drugs like lidocaine and bupivacaine have a lower cost and is abundantly available (Carpenter et al., 2004). Lidocaine is an amide anaesthetic that blocks sodium/calcium channels (Ortega and Cruz, 2011). Tramadol is another narcotic drug used for analgesic purposes in small animals after surgery (Morgaz et al., 2013). This drug is a synthetic analogue of codeine (Mastrocinque and Fantoni, 2003; Morgaz et al., 2013). Its analgesic effect is one-tenth that of morphine (Saberi Afshar et al., 2017); moreover tramadol involves a lower respiratory depression compared with morphine (Mastrocinque and Fantoni, 2003). To the

best of the author's knowledge, no published paper has examined the analgesic effects of the combined intraperitoneal administration of topical anaesthetics and opioid analgesics. Accordingly, the objective of the present study was to investigate the effectiveness of the combined intraperitoneal use of lidocaine and tramadol on pain control after ovariohysterectomy in dogs.

2 | MATERIALS AND METHODS

The project was approved by the local Committee of the Institutional Animal Care and Use of *** (no. ***).

2.1 | Animals

This research was carried out on 18 clinically healthy female mixed-breed dogs with an age range of 1–2 years and weight of 16.7 ± 3.8 kg. The dogs were research animals which belonged to the ***. The health status of all animals was confirmed by clinical examination and blood cell count and determining the total protein level. The animals were kept in the same conditions and had access to enough water and food. They were randomly assigned to three equal groups, lidocaine (L), tramadol (T) and lidocaine-tramadol (LT) groups. The dogs were counted and the numbers were selected by withdrawing a lot from a box. The treatment was then randomly selected using the same method. The food and water were withheld for 12 and 2 hr, respectively, prior to the experiment. They were housed individually and fed on a commercial diet.

2.2 | Procedure

Initially, the dogs were sedated with intramuscular administration of acepromazine 1% (0.05 mg/kg) (Grimm et al., 2015). Thirty minutes later, an angiocatheter (No. 20) was inserted into both the cephalic vein, and the abdominal area was clipped to perform ovariohysterectomy. Following 10 min (40 min after sedation), anaesthesia was induced through titration with diazepam (0.5 mg/kg) and ketamine (10 mg/kg) (Grimm et al., 2015). Next, endotracheal intubation was done. To maintain anaesthesia, the animals were connected to an inhaled anaesthetic device equipped with an isoflurane vaporizer. Isoflurane was further administered at a concentration of 1.5% and an oxygen flow of 1.5 L. Anaesthesia continued until the skin was closed. To keep track of the condition and depth of anaesthesia, the vital parameters were evaluated every five minutes, but they were not recorded as work results. In addition, ketoprofen (2 mg/kg) (Lemke et al., 2002) and cefazolin (10 mg/kg) were administered intravenously immediately before surgery. Ringer's solution was also administered at a rate of $10 \text{ ml kg}^{-1} \text{ hr}^{-1}$ hour during the surgery. Ovariohysterectomy was performed by a regular team. Before closing the linea alba, the drugs were intraperitoneally administered to each group as a splash on the viscera of the abdominal area. For

this purpose, lidocaine containing 0.08 mg/ml epinephrine (8.8 mg/kg) was administered in group L (Carpenter et al., 2004), tramadol (4 mg/kg) in group T (Evangelista et al., 2014) and lidocaine containing epinephrine (8.8 mg/kg) plus tramadol (4 mg/kg) in the LT group. The final injection volume was 0.2 ml/kg (Campagnol et al., 2012). Cefazolin (10 mg/kg, intramuscularly) was administered every 12 hr for three days after surgery. Pain was scored and vital signs (respiratory rate, heart rate and rectal temperature) were recorded 30 min, 1, 3, 6, 12 and 24 hr after extubation.

The following pain scoring systems were evaluated: modified form of subjective pain assessment system (Sammarco Method) (Sammarco et al., 1996; Groppetti et al., 2011), descriptive pain assessment methods simple descriptive score (SDS), the University of Melbourne pain scale (UMPS) (Saber Afshar et al., 2017), and short-form Glasgow composite measure pain scale (CMPS-SF) (Reid et al., 2007). Dogs with a CMPS-SF score of more than 6 out of 24 or 5 out of 20 (Lambertini et al., 2018) were administered with morphine intramuscularly at a dose of 0.5 mg/kg (Campagnol et al., 2012). If necessary, an analgesic dose was given, and the animal data of the recipient were included in the study results. To prevent any individual error, scoring was recorded by two investigators who were blind to the treatments.

To measure the serum levels of cortisol (ELISA method, Commercial Kit, ***), glucose, and total protein (Colorimetric assay kits, ***), blood samples were taken at different time points, including before sedative administration, before intraperitoneal administration, and 1, 3 and 6 hr after extubation. The sera were stored at -70°C until the evaluation day.

2.3 | Statistical analysis

IBM SPSS software Version 23 (SPSS Inc.) was used for data analysis. To do so, one-way analysis of variance (ANOVA) and the *Kruskal-Wallis test* were performed to compare the data between the groups. A repeated-measures ANOVA test with least significant difference post hoc test and Friedman test were conducted to analyse the physiologic data and sedation scores within each treatment. Wilcoxon signed-rank tests on different combinations of related groups with a Bonferroni adjustment were also employed as Friedman post hoc. Data were presented as mean \pm SE. The level of significance was defined as $p < .05$.

3 | RESULTS

The weight of the animals and the length of the surgery were not statistically different among the studied groups. The duration of recovery from anaesthesia was significantly longer in the LT group than in the L ($p = .001$) and T (0.028) groups (Table 1). Except for 1 and 3 hr after surgery, there were no statistically significant differences in heart rate among the groups. One hour after surgery, the heart rate in the L group was significantly higher than in the T ($p = .015$) and LT ($p = .046$) groups (Table 2). The L group had a significantly higher heart rate compared with the LT group, 3 ($p = .005$) and 6 hr ($p = .030$) after surgery (Table 2). No statistically significant difference was observed among the groups concerning the respiratory rate (Tables 2). The evaluation of rectal temperature at the time of the study showed no statistically significant difference among the three groups (Tables 2). Cortisol levels in the LT group exhibited a significant decrease compared to L group ($p = .010$) 3 hr and to the L and T groups, 1 ($p = .004$, 0.005) and 6 ($p = .001$, .006) hours after surgery ($p \leq .05$) (Table 3). No statistically significant difference was observed in the serum glucose and total protein levels (Tables 3). No statistically significant difference was recorded in SDS and Sammarco method between the groups. (Tables 4). UMPS pain assessment showed significant changes during the study time. In this connection, 30 min ($p = .004$, 0.043), 1 ($p = .000$, 0.018) and 24 ($p = .042$, 0.043) hours after surgery, the pain scores in the LT group were significantly lower than in lidocaine (L) and the tramadol (T) groups. Furthermore, in the LT group, the pain scores were significantly reduced 3 ($p = .001$), 6 ($p = .007$), and ($p = .020$) 12 hr after surgery compared to the L group ($p \leq .05$) (Tables 4). Statistically, CMPS-SF pain score was lower in the LT group than in L and T groups, 1 ($p = .003$, 0.013), 12 ($p = .008$, 0.003) and 24 ($p = .026$, 0.008) hours after surgery. The LT group had significantly reduced pain scores 30 min ($p = .001$), 3 ($p = .005$) and 6 ($p = .003$) hours post surgery compared to the L group (Tables 4). Morphine was not required in any of the groups during the first three evaluation periods (30 min, 1, and 3 hr following surgery). The frequency of morphine administration 6, 12 and 24 hr after surgery was not significant between the study groups. The general administration frequency of analgesics was significant regardless of the time of administration in the L group (eight times) compared to T group (three times), $p = .011$ and T group (one time), $p = .001$ ($p \leq .05$). (Tables 5).

Parameter/Groups	L	T	LT
Weight (kg)	17.33 \pm 4.00	15.02 \pm 1.35	17.95 \pm 4.12
Surgery duration (min)	29.00 \pm 4.18	31.25 \pm 2.93	30.40 \pm 31.25
Recovery duration (min)	63.00 \pm 17.88 LT	80.12 \pm 14.14 LT	105.02 \pm 11.18 L, T

TABLE 1 Mean \pm SD of weight, surgery duration and recovery duration in 18 dogs undergoing ovariohysterectomy and intraperitoneal administration of 8.8 mg/kg of lidocaine (L), 4 mg/kg Tramadol (T) or lidocaine (8.8 mg/kg)-Tramadol (4 mg/kg) (LT)

Note: The name of the group listed at the top of the numbers indicates a significant difference with that group ($p < .05$).

TABLE 2 Vital signs result as mean \pm SD in 18 dogs before and after intraperitoneal administration of 8.8 mg/kg of lidocaine (L), 4 mg/kg Tramadol (T) or lidocaine (8.8 mg/kg)-Tramadol (4 mg/kg) (LT) undergoing ovariohysterectomy

Parameters	Group/Times	Before surgery		After surgery		1 hr	3 hr	6 hr	12 hr	24 hr
		30 min ^(a)	30 min ^(b)	30 min ^(b)	30 min ^(b)					
Heart rate (beats / min)	L	90.8 \pm 11.3	112.6 \pm 8.7	114.0 \pm 12.2	116.8 \pm 8.3 LT ^a	120.2 \pm 7.5 LT ^a	113.0 \pm 12.3 ^a	92.4 \pm 14.8		
	T	90.0 \pm 13.2	109.7 \pm 7.9	83.7 \pm 6.9 L ^b	98.2 \pm 10.1	111.5 \pm 6.6 ^a	106.1 \pm 10.4	113.0 \pm 11.7		
Respiratory rate (rate / min)	LT	92.0 \pm 8.1	102.5 \pm 10.2	94.3 \pm 9.1 L	76.2 \pm 12.0 L	100.0 \pm 13.2 L	93.2 \pm 11.3	96.6 \pm 10.6		
	L	22.0 \pm 1.5	21.5 \pm 4.0	24.0 \pm 3.2	23.3 \pm 3.0	24.6 \pm 1.2	25.2 \pm 4.4	26.0 \pm 5.1		
Rectal Temperature (°C)	T	20.6 \pm 1.2	17.5 \pm 2.2	16.7 \pm 1.8	19.5 \pm 3.1	20.5 \pm 1.9	21.4 \pm 1.7	23.0 \pm 1.2		
	LT	21.6 \pm 1.3	23.1 \pm 4.3	24.0 \pm 7.1	26.0 \pm 2.0 ^a	23.5 \pm 6.1	21.3 \pm 1.2	25.2 \pm 4.8		
Rectal Temperature (°C)	L	37.76 \pm 0.33 ^b	36.62 \pm 0.84 ^a	36.56 \pm 0.60 ^a	37.00 \pm 1.12	37.88 \pm 0.42	38.08 \pm 0.36 ^b	38.06 \pm 0.71 ^b		
	T	37.55 \pm 0.60	37.34 \pm 0.91	36.02 \pm 1.00 ^a	36.47 \pm 1.28	37.52 \pm 1.83	38.21 \pm 0.51	38.42 \pm 0.92		
	LT	37.66 \pm 0.57	36.14 \pm 1.34	36.60 \pm 1.32	36.45 \pm 1.21	37.36 \pm 0.28	37.86 \pm 0.42	38.32 \pm 0.59 ^b		

Note: The name of the group listed at the top of the numbers indicates a significant difference with that group ($p < .05$).

^aDifferent letters in each row indicate a significant difference with the time before surgery in each group ($p < .05$).

^bDifferent letters in each row indicate a significant difference with the time before ip in each group ($p < .05$).

4 | DISCUSSION

Postoperative pain relief in patients is not only ethically important, but also helps prevent the harmful physiological effects of pain (Hansen, 2005). In this study, ovariohysterectomy was studied as a causative agent. Postoperative pain following ovariohysterectomy is in moderate category (Carpenter et al., 2004; Hardie et al., 1997). In the present study, meanwhile, the intraperitoneal method was utilized to prescribe analgesics. Numerous studies have assessed the effectiveness of intraperitoneal administration and have explicitly stated that the intraperitoneal administration of local anaesthetics is a valuable and approved method for controlling postoperative pain (Chilkot et al., 2019).

It has been proposed that the effectiveness of tramadol is dependent on the period of pain caused by nerve damage and that its analgesic may change over time (Hama & Sagen, 2007). Lack of a uniform anatomy of the peripheral nervous system and the difference between various types of nerve fibres in local anaesthesia sensitivity may explain the conflicting results obtained from the intraperitoneal administration of tramadol (Akinici et al.,). In 2004, Carpenter et al. performed the combined intraperitoneal and subcutaneous administration of lidocaine 2% (8.8 mg/kg), bupivacaine 0.75% (4.4 mg/kg) for pain relief after ovariohysterectomy in dogs; they reported that bupivacaine was more effective (Carpenter et al., 2004). Intraperitoneal administration of bupivacaine in humans following ovariohysterectomy has also been effective (Ng et al., 2002). Intraperitoneal administration of bupivacaine has been reported effective in managing postoperative ovariohysterectomy in dogs (Campagnol et al., 2012; Guerrero et al., 2016; Lambertini et al., 2018). In 2004, Wilson et al. Studied the pharmacokinetics of 2% lidocaine in intravenous (8.8 mg/kg) and incisional (2 mg/kg) forms in dogs undergone OHE. They concluded that the administration of lidocaine with epinephrine intravenously was safe at the studied dose. One of the advantages of this drug is that it is relatively inexpensive and uncontrolled. Furthermore, the intravenous injection of this drug at higher doses can be prescribed without risk, possibly augmenting the duration of the effect. Also, Campagnol et al. (2012) compared the injection of bupivacaine into intrahepatic and incisional forms. Their study was performed on 30 dogs divided into three groups, each including 10 dogs. After 24 hr, pain relief was occurred on seven dogs in the control group, five dogs in the incisional (INC) group, and three dogs in the intrahepatic group. Dogs receiving intraperitoneal bupivacaine experienced less pain in the first hour after the removal of tracheal tube. A larger dose of topical anaesthetic was required for intraperitoneal anaesthesia; thus, the bupivacaine dose used in the intraperitoneal group was five times higher than that in the INC group. The findings of their study revealed no advantage associated with pre-incision anaesthesia with bupivacaine. Moreover the administration of bupivacaine in the intraperitoneal route before ovariohysterectomy reduced the pain intensity in the first hour after surgery (Campagnol et al., 2012). Intraperitoneal administration of ropivacaine (3.3 mg/kg) has also been effective after ovariohysterectomy in dogs (Lambertini et al., 2018). In another study, after the laparoscopic removal of the gallbladder in humans, the combined

TABLE 3 Blood parameters result as mean \pm SD in 18 dogs before and after intraperitoneal administration of 8.8 mg/kg of lidocaine (L), 4 mg/kg Tramadol (T) or lidocaine (8.8 mg/kg)-Tramadol (4 mg/kg) (LT) undergoing ovariectomy

Parameters	Group/ Times	Before surgery	Before ip administration	After surgery		
		30 min ^(a)	5 min ^(b)	1 hr	3 hr	6 hr
Cortisol (μ g/dl)	L	5.18 \pm 1.80	11.60 \pm 1.12	7.49 \pm 2.36LT ^b	8.17 \pm 1.94 T, LT ^b	8.10 \pm 1.36LT ^b
	T	4.07 \pm 1.43 ^b	11.65 \pm 2.71 ^a	7.29 \pm 0.51LT	6.44 \pm 0.86 L ^b	6.90 \pm 1.75LT
	LT	4.39 \pm 1.37 ^b	10.55 \pm 1.06 ^a	3.01 \pm 0.68L, T ^b	3.53 \pm 1.11L ^b	2.94 \pm 0.91L,T ^b
Glucose (mg/dl)	L	87.50 \pm 5.97 ^b	101.00 \pm 3.70 ^a	86.25 \pm 9.81 ^a	90.66 \pm 6.92	99.25 \pm 7.40
	T	92.25 \pm 6.83	106.75 \pm 4.01	86.66 \pm 7.63	92.00 \pm 8.71	105.50 \pm 8.31
	LT	87.75 \pm 5.90	100.75 \pm 7.24	83.50 \pm 8.22	87.75 \pm 6.72	104.25 \pm 7.51
Total protein (g/dl)	L	6.30 \pm 0.27	6.05 \pm 0.58	5.82 \pm 0.96	5.55 \pm 0.94	5.92 \pm 0.60
	T	6.54 \pm 0.43	5.75 \pm 0.91	5.02 \pm 0.76 ^a	5.45 \pm 0.68 ^a	6.02 \pm 0.93
	LT	6.45 \pm 0.85 ^b	5.52 \pm 0.71 ^a	5.12 \pm 0.44 ^a	5.32 \pm 0.34 ^a	5.47 \pm 0.32 ^a

Note: The name of the group listed at the top of the numbers indicates a significant difference with that group ($p < .05$).

^aDifferent letters in each row indicate a significant difference with the time before surgery in each group ($p < .05$).

^bDifferent letters in each row indicate a significant difference with the time before ip in each group ($p < .05$).

intraperitoneal administration of bupivacaine and tramadol resulted in inadequate analgesia (Golubovic et al., 2009). In 2008, Akinc et al. showed that after the laparoscopic removal of the gallbladder by intravenous or intraperitoneal administration of tramadol, intravenous tramadol was more intraperitoneal tramadol (Akinci et al., 2008).

In this study, lidocaine was intraperitoneally administered with tramadol. Intraperitoneal administration of analgesics in combination with topical anaesthetics causes a good deal of awakening in humans. It was reported that the intraperitoneal addition of morphine to bupivacaine resulted in appropriate pain relief after

TABLE 4 Pain Scoring results as mean \pm SD in 18 dogs before and after intraperitoneal administration of 8.8 mg/kg of lidocaine (L), 4 mg/kg Tramadol (T) or lidocaine (8.8 mg/kg)-Tramadol (4 mg/kg) (LT) undergoing ovariectomy

Parameters	Group/ Times	After surgery					
		30 min ^(a)	1 hr	3 hr	6 hr	12 hr	24 hr
SDS (0-3)	L	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-2)	2 (0-3) ^a	2 (0-3)
	T	0 (0-0)	0 (0-3)	0 (0-1)	0 (0-3)	1 (0-3)	1 (0-3)
	LT	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)
Sammarco (0-24)	L	1 (0-1)	3 (0-6)	6 (4-9) ^a	6 (5-7) ^a	7 (6-7) ^a	7 (6-8) ^a
	T	0 (0-1)	1 (0-1)	6 (3-7) ^a	6 (6-8) ^a	6 (6-9) ^a	6 (4-7) ^a
	LT	0 (0-2)	1 (0-6)	5 (2-8) ^a	6 (5-7) ^a	5 (5-7) ^a	6 (4-6) ^a
UMPS (0-25)	L	3 (1-4) ^{LT}	3.5 (3-6) ^{T,LT}	4.5 (3-8) ^{T,LT}	4 (3-6) ^{LT}	4.5 (3-8) ^{LT^a}	3 (1-6) ^{LT^a}
	T	2.5 (1-3) ^{LT}	2.5 (2-3) ^{L,LT}	2.5 (2-3) ^L	3.5 (2-4)	4 (2-6)	4 (2-4) ^{LT}
	LT	1 (0-2) ^{L, T}	1 (0-2) ^{L, T}	2 (1-2) ^L	2.5 (1-3) ^L	2.5 (2-4) ^{L^a}	2 (1-2) ^{L, T^a}
Glasgow CMPS-SF (0-24)	L	3.5 (2-4) ^{T,LT}	3.5 (1-4) ^{LT}	4 (2-5) ^{T,LT}	4 (3-6) ^{LT}	5.5 (0-9) ^{LT}	3 (2-4) ^{LT}
	T	2 (1-2) ^L	3 (2-3) ^{LT}	2.5 (1-3) ^L	3 (1-5)	6 (4-9) ^{LT^a}	3.5 (2-7) ^{LT}
	LT	1 (1-2) ^L	1 (1-2) ^{L, T}	(1-3) ^L	0.5 (0-3) ^L	0 (0-3) ^{L, T}	0 (0-3) ^{L, T}

Note: The name of the group listed at the top of the numbers indicates a significant difference with that group ($p < .05$).

^aDifferent letters in each row indicate a significant difference with the time before surgery in each group ($p < .05$).

^bDifferent letters in each row indicate a significant difference with the time before ip in each group ($p < .05$).

TABLE 5 Numbers of dogs received morphine (0.5 mg/kg, IM) in 18 dogs before and after intraperitoneal administration of 8.8 mg/kg of lidocaine (L), 4 mg/kg Tramadol (T) or lidocaine (8.8 mg/kg)-Tramadol (4 mg/kg) (LT) undergoing ovariectomy

Groups/Times	After surgery						Total
	30 min (a)	1 hr	3 hr	6 hr	12 hr	24 hr	
L	0	0	0	2	4	2	8T, LT
T	0	0	0	1	1	1	3 L
LT	0	0	0	0	1	0	1 L

Note: The name of the group listed at the top of the numbers indicates a significant difference with that group ($p < .05$).

the laparoscopic removal of the gallbladder (Hernandes-Palazon et al., 2003). Furthermore, tramadol intraperitoneally added to bupivacaine led to appropriate pain relief after laparoscopic uterine ligator surgery in humans (Memis, 2005). In several studies, researchers have reported tramadol local anaesthesia with very few side effects (Altunkaya et al., 2003; Altunkaya et al., 2004; Robaux et al., 2004). Intraperitoneal administration is a risk-free, inexpensive, and non-invasive procedure that can be easily performed. In the intraperitoneal method, higher doses can be administered compared with the intravenous method, possibly increasing the duration of the effect (Karsli et al., 2003; Wilson et al., 2004). Surgical procedures cause stress in living organisms as they involve tolerance, medication, anaesthesia, and hospitalization. The stress caused by pain has been evaluated by several clinical and hormonal markers, including cortisol measurement and behavioural assessments (Nenadović et al., 2017). In the current research, several analyses were performed to evaluate the effectiveness of the combined intraperitoneal administration of lidocaine and tramadol, which are discussed below.

Cortisol level assessment revealed no statistically significant difference between the groups at baseline and five minutes before drug administration. However, significant changes were detected at all times after the drug was administered. Cortisol levels in the LT group were significantly lower than that in other groups ($p < .05$). Tissue damage causes pain and increases the cortisol levels through activating the hypothalamic-pituitary-adrenal axis. (Fazio et al., 2015; Nenadović et al., 2017). As a common marker of surgical stress, cortisol has been reported to increase in various surgical procedures, including anaesthesia procedures. Increased cortisol levels during surgery are due to tissue damage, which is more prevalent in abdominal surgery than in surface surgery (Evangelista et al., 2014; Fazio et al., 2015; Fox et al., 1994; Gutiérrez-Bautista et al., 2018; Nenadović et al., 2017). Shutt et al. (2003) showed that plasma cortisol levels increased due to postoperative pain, which is consistent with the findings of the present study. The significant reduction in cortisol levels in the LT group at all time points after drug administration might be indicative of less pain perception, more pain suppression with administered medications, and greater patient relaxation in the current study.

Additionally, measuring and comparing the glucose levels among the studied groups did not reveal any statistically significant difference. As a stressor, pain can be associated with augmented glucose

concentrations, and the changes in such concentrations can specify the effectiveness of analgesics (Martins et al., 2010). Pain increases the amount of glucose via upsetting the balance of the hypothalamic-pituitary-adrenal axis and impacting the adrenal glands; hence, this parameter can further be employed as an auxiliary tool for tracking pain. The increase in glucose levels also reduces pain tolerance (Morley et al., 1984) while increased glucose levels can raise the pain intensity (Cradock & Hawthorn, 2002). Cortisol did not significantly change in this study, so the comparison of cortisol levels can be disarmed. However, this study considered glucose to be an interfering factor which might make the results more valuable.

Moreover we measured the amount of total protein to assess the status of possible hydration/dehydration as an intervening factor so that its reduction would question the increase in other parameters. In a sense, this parameter indicates a patient's health status. Measurement of total serum protein showed no statistically significant difference between the studied groups. Also, as mentioned earlier, it revealed the appropriate state of hydration/dehydration and confirmed the acceptability of other parameters. Meanwhile, one of the side effects of pain is the increased protein catabolism (Mastrocinque and Fantoni, 2003; Morgaz et al., 2014); no significant changes in this parameter indicates relatively stable pain conditions. Comparison of the heart rates displayed no statistically significant differences, except for one and three hours after surgery, where the L group had significantly higher rates than other groups. This increase in heart rate, although within the normal range of heart rate, may be attributed to greater pain tolerance in animals in this group. One point that reinforces this hypothesis is that at the same time, cortisol levels in the L group were higher than that in the LT group. Due to the concurrent rise in cortisol level and higher score of pain in UMPS and Glasgow scoring in some times, it was considered close to the fact that animals in the L group suffered from more pain. Furthermore, in the present study, changes in the respiratory rate did not show any statistically significant differences between the studied groups. Also, the changes in anal temperature did not have any statistically significant difference between the groups under study. No statistically significant differences were observed among the groups in terms of the changes in pain scoring with SDS and Sammarco methods. On the other hand, the changes in pain scoring with the UMPS and Glasgow methods in this study showed a significant reduction in pain scores in the LT group compared to other groups and at all evaluation time points. Details of these changes are presented in Table 4.

In this study, the modified form of Sammarco's et al.'s pain assessment system (1996) was employed to evaluate postoperative pain in the studied animals. In this pain assessment system, pain grading is based on six categories of behaviour, namely comfort, mobility, appearance, unreasonable and irrelevant behaviour, interaction and noise. Each category of behaviour is divided into smaller levels, rated from zero to 4 in line with the lowest to the highest pain rating. In this way, the maximum score available for each animal will be 24. We also evaluated the SDS scale which is easy to use but has a poor sensitivity (Holton et al., 2001). The main problem with SDS is that it is not a sensitive scale for measuring pain as it consists of four or five subgroups, and observer bias may play a key role in determining the pain scale (Saber Afshar et al., 2017).

Hellyer et al. used UMPS, which is a more objective method as it uses such physiological data as heart rate and respiration. In 2007, Reid et al. claimed that the Melbourne scale was highly effective in clinical use. The Glasgow pain scale is a behavioural approach to assessing acute pain. This scale is more accurate than other methods of pain assessment because it is based on the principles of animal behaviour (Reid et al., 2007). Therefore, in several studies, Glasgow pain scale has been the ultimate criterion for assessing pain and prescribing analgesics (Gutiérrez-Bautista et al., 2018; Lambertini et al., 2018).

5 | CONCLUSION

According to the results, it seems that the combination of lidocaine and tramadol can provide better analgesia than their separate use. Meanwhile, in this study, no adverse effects were observed clinically or in vital signs. Hence, we recommend the combined intraperitoneal administration of lidocaine (8.8 mg/kg) and tramadol (4 mg/kg) with a final volume (0.2 ml/kg) following ovariohysterectomy in dogs.

ETHICAL ANIMAL RESEARCH

The project was approved by the local Committee of the Institutional Animal Care and Use of Shahid Chamran University of Ahvaz, Ahvaz, Iran.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

Behnam Farokhzad: Investigation; Visualization. **Soroush Sabiza:** Methodology; Supervision. **Mohammad Razi Jalali:** Formal analysis; Methodology. **Ali Baniadam:** Data curation; Methodology.

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