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## Postoperative pain assessment with concurrent administration of intraperitoneal tramadol and incisional lidocaine following ovariohysterectomy in dogs

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**ABSTRACT:** This study aimed to assess postoperative pain with concurrent administration of intraperitoneal tramadol and incisional lidocaine following ovariohysterectomy in dogs. A group of twenty mixed breed female dogs, aged 1-2 years, weighing  $19.5 \pm 0.8$  kg were used. Initially, dogs were sedated with intramuscular administration of acepromazine 1%. Anaesthesia was induced with diazepam (0.5 mg/kg) and ketamine (10 mg/kg) and maintained with 1.5% Isoflurane. Ketoprofen (2 mg/kg) was administered intravenously just before the initiation of the surgery. Five minutes before midline incision, saline (0.2 ml/kg) was injected to the muscles and subcutaneous space around the incision in the tramadol-saline (TS) group. Also, in the tramadol-lidocaine (TL) group, lidocaine 2% with epinephrine (1.5 mg/Kg) was administered subcutaneously. Ovariohysterectomy was performed and before closing the linea alba, tramadol (4 mg/kg) was splashed on the abdominal viscera in both groups. Cortisol, vital signs and pain scoring systems were evaluated at different time points. Heart rate, respiratory rate and rectal temperature changes were not statistically significant between groups. Cortisol level showed a significant difference between groups at 1, 3 and 6 hours after surgery ( $p \leq 0.05$ ). Both UMPS and CMPS-SF pain scores in the TL group were significantly lower than the TS group at 30 minutes, 1, 3 and 6 hours after surgery ( $p \leq 0.05$ ) and also at 12 hours after surgery ( $p \leq 0.05$ ). It seems that intraperitoneal administration of tramadol (4 mg/kg) along with administration of incisional lidocaine with epinephrine (1.5 mg/kg) is recommended following ovariohysterectomy in dogs.

**Keywords:** dog, intraperitoneal tramadol, incisional lidocaine, ovariohysterectomy.

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## INTRODUCTION

Pain is an unpleasant sensation associated with actual or potential tissue damage (Wright & Aydede 2017). Postoperative pain has many adverse effects such as decreased food intake, increased protein catabolism, impaired respiratory function, irregular heart rhythm, increased central sensitivity to painful stimuli, increased postoperative stress, suppressed immune system, increased arterial blood pressure, delayed wound healing, and inconsistent behaviors, including self-attack (Gwendolyn and Carrol, 1996; Gaynor, 1999; Flecknell and Watermen-Pearson, 2000). Effective and better pain management is achieved when multiple analgesics are used to target multiple pain pathways (Hellyer et al., 2007; Reuben et al., 2007). Post-operatively abdominal pain usually occurs within the first 24 hours (Golubovic et al., 2009). In the other, ovariohysterectomy is one of the most common surgeries in small animals. Pain after ovariohysterectomy is classified as mild to moderate (Hardie et al., 1997; Carpenter et al., 2004). A way to induce appropriate analgesia in ovariohysterectomy is to combine local anaesthesia with systemic analgesics (Slingsby et al., 2008; Gurney et al., 2012). Intraperitoneal administration of local anaesthetics or analgesics is a valuable and proven method for pain control after abdominal surgery in human and veterinary medicine (Golubovic et al., 2009; Chilkoti et al., 2019). Although intraperitoneal analgesia can block pain transmitters in visceral structures, it does not prevent pain transmission to areas close to the skin. Similarly, local anaesthesia around an incision that prevents pain in the superficial areas cannot block visceral pain (Ng et al., 2002). As topical analgesics have mild systemic effects, concomitant intraperitoneal administration of analgesia in abdominal surgery can optimally control pain with minimal side effects (Marks et al., 2012). Tramadol is a synthetic analogue of codeine, narcotic drug used for analgesic purposes after surgery in small animals (Mastrocinque and Fantoni, 2003; Morgaz et al., 2013). Its analgesic effect is the one-tenth of morphine and it less affects the respiratory function than morphine (Mastrocinque and Fantoni, 2003). Numerous clinical studies have shown suitable postoperative pain management concomitant administration of opioid drugs such as tramadol intraperitoneally and local anaesthetics, following open or laparoscopic abdominal surgery in humans (Karsli et al., 2003; Memis et al., 2005; Golubovic et al., 2009). Local anaesthesia is very diverse due to its clinical applications. This group of drugs usually

anaesthetizes a block of nerves or the spinal through infiltration, by inhibiting pain transmitters (Skarda and Tranquilli, 2007). Lidocaine is a local anesthetic which blocks the sodium-calcium channel (Fozzard et al., 2005) and inhibits neurons associated with visceral pain (Ortega and Cruz, 2011). Various studies have shown that intraperitoneal administration and/or around the incision site of lidocaine or bupivacaine is sufficient for analgesia after ovarian hysterectomy in dogs (Carpenter et al., 2004; Campagnol et al., 2012; Guerrero et al., 2016; Lambertini et al., 2018; Chilkoti et al., 2019). Using peripheral and intraperitoneal lidocaine in cat ovarian surgery, it was showed that this method enhances postoperative analgesia (Zilberstein et al., 2008). According to the literature, there is no published data about the analgesic effects of concomitant administration of intraperitoneal tramadol and lidocaine around the incision site. Therefore, this study aimed to evaluate the effectiveness of concomitant administration of lidocaine around the incision and tramadol intraperitoneally to manage post-operatively pain after ovariohysterectomy in dogs.

## MATERIALS AND METHODS

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

### Animals

This study was carried out on twenty clinically healthy female mixed-breed dogs ranged in age from 1-2 years and weighted  $19.55 \pm 0.8$  kg. The health status of all animals confirmed with clinical examination and blood cell counts, and total protein level. The animals were kept in the same conditions and had access to enough water and food. The animals were randomly assigned to two equal groups, tramadol-saline (TS) and tramadol-lidocaine (TL) groups. Food was withheld for 12 hours and water for 2 hours before the experiment. They were housed individually and fed on a commercial diet.

### Procedure

Initially, dogs were sedated with intramuscular administration of 0.05 mg/kg acepromazine 1% (Alfasan, Neatherland) (Grimm et al., 2015). Thirty minutes later, an intravenous catheter (No. 20) was inserted into the cephalic vein and the abdominal area was clipped to perform ovariohysterectomy. After 10 minutes (40 minutes after sedation), anaesthesia was induced through titration with diazepam (0.5 mg/kg)

and ketamine (10 mg/kg) (Grimm et al., 2015). Then, endotracheal intubation was performed. To maintain anaesthesia, the animals were connected to an inhaled anaesthetic device equipped with an isoflurane vaporizer. Isoflurane was administered at a concentration of 1.5% and an oxygen flow at a rate of 1.5 litres. Anaesthesia was maintained until the skin was closed. During the anaesthesia period and to be aware of the patient's condition and the depth of anaesthesia, the vital parameters were evaluated every five minutes but they were not recorded as results of the work. Furthermore, ketoprofen (2 mg/kg) (Lemke et al., 2002) and cefazolin (10 mg/kg) were administered intravenously immediately before surgery. Ringer's solution was also administrated during the surgery at a rate of 10 ml/kg/hr.

Five minutes before midline abdominal incision, saline (0.2 ml/kg) (Campagnol et al., 2012) was administered to the muscles and subcutaneous space around the incision in the TS group. Also, in the TL group, lidocaine 2% containing epinephrine (1.5 mg/Kg) was administered with the same route as in the TS group. The final volume of the injections was 0.2 ml/kg (Vicente et al. 2012). Then, ovariohysterectomy was performed by a regular team blinded concerning the groups. Before closing the white line, tramadol (4 mg/kg) with the final volume of (0.2 ml/kg) (Campagnol et al., 2012) was splashed on the viscera of the abdominal area in both groups. After surgery, cefazolin (10 mg/kg intramuscularly) was given every 12 hours for 3 days.

The pain was scored and vital signs (respiratory rate, heart rate and rectal temperature) were recorded and at 30 minutes, one, three, six, 12 and 24 hours after extubation. To assess patients' sedation status, a score range of zero (without sedation) to three (deep sedation) was used (Lambertini et al. 2018). The following pain scoring systems were assessed: a 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 (Saberi Afshar et al., 2017) and short-form Glasgow Composite Measure Pain Scale (CMPS-SF) (Reid et al., 2007). Dogs with CMPS-SF score more than six out of 24 or five out of 20 (Lambertini et al., 2018), were administered with morphine intramuscularly at a dose of 0.5 mg/kg as a rescue analgesia (Campagnol et al., 2012). If necessary, an analgesic dose was given, and the animal data

of the recipient were included in the study results. It should also be noted that 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, Monobind Inc, Germany), glucose and total protein (Colorimetric assay kits, Pars Azmun, Iran), blood samples were taken at different time points including before sedative administration, before intraperitoneal administration, one, three and six hours after extubation. The sera were stored at -70 °C until the day of evaluation.

### Statistical analysis

IBM SPSS Version 23 (SPSS Inc.; IL, USA) was used for data analysis. An independent samples t test and Mann-Whitney U test were used to compare the physiologic values and sedation scores between treatments, respectively. A repeated measure analysis of variance test and Wilcoxon signed rank test were used to analyze the physiologic data and sedation scores within each treatment, respectively. Data were presented as mean  $\pm$  standard error. The level of significance was defined as  $p < 0.05$ .

### RESULTS

The age of all animals was selected in the range of 1-2 years. The weight of the animals, the duration of surgery and anaesthesia recovery did not show a statistically significant difference between the groups (Table 1). There was not a significant difference in the heart rate between the study groups and also in the study times in each group, in the study times after surgery compared to the baseline time (Table 2). Comparing respiratory rates between the studied groups did not show a statistically significant difference (Table 2). The increase in the respiratory rates on each study group was significant in the first hour after surgery compared to the baseline in both groups (TS group,  $p = 0.038$  and TL group,  $p = 0.041$ ) (Table 2). The changes in rectal temperature between the study groups and also in the study times on each group was not statistically significant in the study times after surgery compared to the baseline time (Table 2). According to the data, a significant decrease in serum cortisol levels in the tramadol-lidocaine (TL) group compared to the tramadol-saline (TS) group was observed at times 1 ( $p = 0.049$ ), 3 ( $p = 0.047$ ) and 6 ( $p = 0.023$ ) hours after surgery (Table 2). In tramadol-saline (TS) group, there was a significant increase in serum cortisol levels at 5 minutes before peritoneal

administration ( $p = 0.044$ ) and at times 1 ( $p = 0.001$ ), 3 ( $p = 0.010$ ) and 6 ( $p = 0.024$ ) hours relative to baseline time was observed (Table 2). In the tramadol-lidocaine (TL) group, despite the significant increase in serum cortisol levels, these changes were not significant at any time point compared to baseline (Table 3). There was no statistically significant difference in serum glucose levels in the evaluation and comparison between groups in all studied times (Table 3). In the tramadol-saline (TS) group, an increase in serum glucose levels was observed at all times compared to baseline, which was statistically significant only at 6 hours after surgery compared to baseline ( $p = 0.005$ ) (Table 3). In the tramadol-lidocaine (TL) group, an increase in serum glucose levels was observed at all times points compared to baseline, which was statistically only at 1 ( $p = 0.010$ ) and 6 ( $p = 0.035$ ) hours

after surgery compared to baseline (Table 3). Total protein changes were not significant between groups and also at different time points in each group. SDS and Sammarco pain scores were not significant between groups and also at different time points in each group (Table 4). UMPS pain scores in the TL group were significantly lower than the TS group at 30 minute ( $p=0.043$ ), 1 ( $p=0.04$ ), 3 ( $p=0.041$ ) and 6 ( $p=0.04$ ) hours after surgery (Table 4). Also, CMPS-SF pain scores in the TL group were significantly lower than the TS group at 30 minute ( $p=0.041$ ), 1 ( $p=0.043$ ), 3 ( $p=0.043$ ), 6 ( $p=0.043$ ) and 12 ( $p=0.046$ ) hours after surgery (Table 4). Sedation scores did not show a significant difference between groups (Table 4). There was no need for morphine administration at any time points regarding CMPS-SF pain scores.

**Table 1.** Mean  $\pm$  SE of Weight, surgery duration and recovery duration in twenty dogs before and after *ip* administration of 4 mg kg<sup>-1</sup> Tramadol with SC administration of 0.2 ml kg<sup>-1</sup> Saline (TS) or 1.5 mg kg<sup>-1</sup> lidocaine with epinephrine (diluted to 0.2 ml kg<sup>-1</sup>) (TL) undergoing ovariohysterectomy

Groups / Parameter	Weight (kg)	Surgery duration (min)	Recovery duration (min)
TS	19.7 $\pm$ 1.4	30.3 $\pm$ 2.9	76.6 $\pm$ 8.8
TL	19.6 $\pm$ 1.1	27.0 $\pm$ 2.6	86.7 $\pm$ 3.3

**Table 2.** Vital signs result as mean  $\pm$  SE in twenty dogs before and after *ip* administration of 4 mg kg<sup>-1</sup> Tramadol with SC administration of 0.2 ml kg<sup>-1</sup> Saline (TS) or 1.5 mg kg<sup>-1</sup> lidocaine with epinephrine (diluted to 0.2 ml kg<sup>-1</sup>) (TL) undergoing ovariohysterectomy

Parameters		Before surgery (baseline)	After surgery						
	Group/ Times	30 minutes	30 minutes	1 hour	3 hours	6 hours	12 hours	24 hours	
Hear rate (rate/min)	TS	113.0 ± 4.7	105.0 ± 7.6	114.3 ± 8.3	112.0 ± 6.1	99.6 ± 8.9	106.6 ± 6.6	104.6 ± 5.6	
	TL	115.3 ± 6.3	112.0 ± 7.0	115.2 ± 2.3	104.6 ± 12.4	110.0 ± 6.1	109.0 ± 3.7	97.0 ± 6.2	
Respiratory rate (breath/min)	TS	19.3 ± 1.3	22.6 ± 0.6 †	20.6 ± 0.6	21.0 ± 0.5	18.0 ± 1.1	18.0 ± 1.2	20.0 ± 1.2	
	TL	18.7 ± 1.7	22.0 ± 1.1 †	21.3 ± 2.6	20.7 ± 1.8	20.0 ± 1.2	19.3 ± 0.7	19.3 ± 1.3	
Rectal Temperature (°C)	TS	37.90 ± 0.30	37.20 ± 0.26	36.80 ± 0.51	36.1 ± 0.54	37.36 ± 0.17	37.93 ± 0.31	37.83 ± 0.29	
	TL	38.44 ± 0.55	36.46 ± 0.12	37.10 ± 0.36	37.2 ± 0.35	37.00 ± 0.30	38.23 ± 0.20	38.10 ± 0.17	

† indicates a significant difference compared to baseline ( $P < 0.05$ ).



**Table 3.** Blood parameters result as mean  $\pm$  SE in twenty dogs before and after *ip* administration of 4 mg kg<sup>-1</sup> Tramadol with SC administration of 0.2 ml kg<sup>-1</sup> Saline (TS) or 1.5 mg kg<sup>-1</sup> lidocaine with epinephrine (diluted to 0.2 ml kg<sup>-1</sup>) (TL) undergoing ovariohysterectomy

Parameters	Group/Times	Before surgery (baseline)	Before ip administration	After surgery		
		30 min	5 min	1 hour	3 hours	6 hours
Cortisol ( $\mu$ g/dl)	TS	8.27 $\pm$ 0.95	13.49 $\pm$ 0.53 <sup>†</sup>	12.82 $\pm$ 0.87 * <sup>†</sup>	12.30 $\pm$ 0.97 * <sup>†</sup>	13.54 $\pm$ 0.71 * <sup>†</sup>
	TL	8.67 $\pm$ 0.67	12.16 $\pm$ 0.44	9.61 $\pm$ 0.74	9.37 $\pm$ 0.35	10.56 $\pm$ 0.41
Glucose (mg/dl)	TS	73.33 $\pm$ 3.71	83.00 $\pm$ 6.24	94.33 $\pm$ 8.83	103.00 $\pm$ 9.53 £	90.00 $\pm$ 4.04 <sup>†</sup>
	TL	82.66 $\pm$ 6.17	89.66 $\pm$ 4.63	95.66 $\pm$ 3.75 <sup>†</sup> £	102.33 $\pm$ 5.04	94.33 $\pm$ 4.97 <sup>†</sup>
Total protein (mg/dl)	TS	6.53 $\pm$ 0.52	5.70 $\pm$ 0.30	5.46 $\pm$ 0.38	6.03 $\pm$ 0.29	5.96 $\pm$ 0.26
	TL	6.86 $\pm$ 0.47	6.40 $\pm$ 0.35	6.53 $\pm$ 0.28	6.16 $\pm$ 0.08	6.33 $\pm$ 0.23

\*indicates a significant difference between groups ( $P < 0.05$ ).

<sup>†</sup> indicates a significant difference compared to baseline ( $P < 0.05$ ).

£ indicates a significant difference compared to the time before ip administration ( $P < 0.05$ ).

**Table 4.** Sedation and pain Scoring results as median (minimum-maximum) in twenty dogs before and after *ip* administration of 4 mg kg<sup>-1</sup> Tramadol with SC administration of 0.2 ml kg<sup>-1</sup> Saline (TS) or 1.5 mg kg<sup>-1</sup> lidocaine with epinephrine (diluted to 0.2 ml kg<sup>-1</sup>) (TL) undergoing ovariohysterectomy

Parameters	Group/Times	After surgery					
		30 min (*)	1 hour	3 hours	6 hours	12 hours	24 hours
Sedation	TS	3 (2-3)	3 (2-3)	2 (1-2)	1 (1-2)	2 (1-3)	2 (1-2)
	TL	1 (1-2)	1 (1-2)	2 (1-2)	1 (1-2)	2 (1-2)	1 (1-2)
SDS	TS	0 (0-1)	0 (0-1)	0 (0-2)	0 (0-2)	0 (0-2)	0 (0-1)
	TL	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Sammarco	TS	8 (3-9)	6 (2-9)	5 (2-6)	6 (1-10)	6 (1-11)	6 (1-7)
	TL	3 (0-8)	3 (1-6)	4 (2-6)	6 (1-9)	6 (1-9)	6 (1-9)
UMPS	TS	4 (4-6)	4 (3-6)	4 (4-5)	5 (4-7)	5 (3-7)	3 (2-3)
	TL	0 (0-3) *	1 (0-2) *	2 (1-3) *	2 (1-2) *	2 (2-3)	2 (1-2)
CMPS-SF	TS	5 (3-5)	4 (4-5)	4 (3-4)	4 (3-5)	3 (3-6)	2 (1-3)
	TL	1 (1-2) *	2 (1-2) *	2 (1-2) *	2 (1-2) *	2 (0-2) *	1 (0-2)

\* indicates a significant difference between groups ( $P < 0.05$ ).

## DISCUSSION

In this study, ovariohysterectomy was studied as a causative agent. (Hardie et al., 1997; Carpenter et al., 2004). On the other hand, in this study, the intraperitoneal method was used to prescribe analgesics. It has evaluated that 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 (Chilkoti et al., 2019). In this study, lidocaine was administered concomitantly as a common anaesthetic and tramadol were administered intraperitoneally. Intraperitoneal administration of analgesics in combination with topical anaesthetics causes effective analgesia in humans. Hernandez-Palazon et al., (2003) showed that the addition of morphine to bupivacaine intraperitoneally, causes appropriate pain

relief after laparoscopic removal of the gallbladder, while the addition of tramadol to bupivacaine intraperitoneally causes appropriate pain relief after laparoscopic uterine ligator surgery in humans (Memis et al., 2005). In several studies, researchers have reported the local anaesthetic properties of tramadol opioid drug with low side effects (Altunkaya et al., 2003; Altunkaya et al., 2004; Robaux et al., 2004). Intraperitoneal administration is a risk-free, inexpensive, non-invasive procedure that can be easily performed. On the other hand, in the intraperitoneal method, a higher dose of drugs can be used with confidence than in the intravenous method, which may, in turn, increase the duration of the drug's effect (Karsli et al., 2003; Wilson et al., 2004). Comparing cortisol levels between the studied groups revealed that there was no statistically significant difference between the groups

at baseline time and five minutes before the drug was administered, while at all time points after the drug administration changes were significant. Cortisol levels in the TL group were significantly lower than that of in other groups at times 1 ( $p = 0.049$ ), 3 ( $p = 0.047$ ) and 6 ( $p = 0.023$ ) hours after surgery ( $P < 0.05$ ). Tissue damage causes pain and increases cortisol levels by activating the hypothalamic-pituitary-adrenal axis. (Fazio et al., 2015; Nenadović et al., 2017). Cortisol is a common marker of surgical stress that has been reported to increase in various surgical procedures as well as in anaesthesia procedures. Increased cortisol levels during surgery are due to tissue damage, which is more common in abdominal surgery than in surface surgery (Fox et al., 1994; Evangelista et al., 2014; Fazio et al., 2015; Nenadović et al., 2017; Gutiérrez-Bautista et al., 2018). The study carried out by Shutt et al., (2003) showed that plasma cortisol levels increase due to postoperative pain, which is consistent with the findings of the present study. A significant reduction in cortisol levels in the TL group at all time points after drug administration may be a sign of less pain perception, more pain suppression with prescribed medications, and greater patient relaxation in this study. Additionally, measuring and evaluating the comparison of glucose levels among the studied groups did not indicate any statistically significant difference. Pain as a stressor can be associated with increased glucose concentrations, and changes in these concentrations can be a means of determining the effectiveness of analgesics (Martins et al., 2010). Pain increases the amount of glucose by upsetting the balance of the hypothalamic-pituitary-adrenal axis and affecting the adrenal glands, so this parameter can also be used as an auxiliary tool to track pain. Increasing glucose levels also reduces pain tolerance (Morley et al., 1984). On the one hand, increasing glucose levels can, in turn, increase cortisol levels (Cradock and Hawthorn, 2002). However, this study considered glucose to be an interfering factor which might make the results more valuable.

Moreover, the purpose of measuring the amount of the total protein in this study was to assess the status of possible hydration/dehydration as an intervening factor so that, if reduced, call into question the increase in other parameters. In a way, measuring this parameter is a component of the patient's health sign. Measurement of total serum protein showed no statistically significant difference between the studied groups and, as mentioned earlier, indicated the appropriate state of hydration/dehydration and confirmed

the appropriateness of other parameters. On the other hand, one of the side effects of pain is an increase in protein catabolism (Mastrocinque and Fantoni, 2003; Morgaz et al., 2014), so lack of significant changes in this parameter indicates relatively stable pain condition. Comparison of the heart rate displayed no statistically significant differences, furthermore, in this study, changes in the respiratory rates did not show any statistically significant differences between groups. Also, changes in anal temperature in this study did not have any statistically significant difference between the groups under study. In the current study, no statistically significant differences were observed between the groups considering the changes in pain scoring with SDS and Sammarco methods. On the other hand, changes in pain scoring with the UMPS and Glasgow methods in this study showed a significant reduction in pain scores in the TL group compared to the TS. Carpenter et al. (2004) used two visual analogue scales (VAS) and CPS to assess pain. They found that VAS was a simple way to assess pain, allowing the supervisor to make treatment decisions while CPS was not. Another Melbourne pain assessment scale (UMPS) was used by Hellyer et al, which is a more objective method because it uses some physiological data, such as heart rate and respiration. Hellyer et al., (2007) claimed that the Melbourne scale was highly effective for 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). For this reason, in several studies, the ultimate criterion for assessing pain and administration or not administration analgesics has been the CMPS-SF pain scale (Gutiérrez-Bautista et al., 2018; Lambertini et al., 2018). No need to rescue analgesic showed that the overall postoperative status of the dogs was considered to be suitable.

## CONCLUSION

According to the obtained results and obtaining less pain score (better condition) in TL group than TS group, it seems that intraperitoneal administration of tramadol (4 mg/kg) along with administration of incisional lidocaine with epinephrine (1.5 mg/kg) is recommended following ovariohysterectomy in dogs.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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