Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
Accessible at: www.pvj.com.pk

RESEARCH ARTICLE

Analgesic Effects of Lidocaine and Fentanyl Alone or in Combination Undergoing Ovariohysterectomy in Female Dogs

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ARTICLE HISTORY (15-510)

Received: December 18, 2015
Revised: February 19, 2016
Accepted: March 13, 2016
Published online: October 15, 2016

Key words:
Canine
Fentanyl
Lidocaine
Ovariohysterectomy
Physiological parameters

ABSTRACT

In this study, the analgesia effects of intravenous injection either of lidocaine, fentanyl, or their combination were compared in dogs undergoing ovariohysterectomy. Forty-eight dogs were randomly assigned into three groups. Anesthesia was induced with 6 mg/kg propofol and maintained with 2% (vaporizer dial setting) isoflurane. Animals received lidocaine (4 mg/kg), fentanyl (3 µg/kg), and their combination after 15 minutes of induction. Heart rhythm, respiratory rhythm, blood pressure, rectal temperature, subjective pain scores and arterial blood-gas were measured at same time. Cardiopulmonary variables changed after injection, and some of them had significant differences compared with baselines at the moment of extubation. The maximal subjective pain scores were recorded at three hours after extubation, but rescue analgesic was not required at this study. Though values regarding blood gas changed after intravenous administration of agents, significant differences were not found between groups at any of the time-points. Both drugs and their combination provided adequate analgesia undergoing ovariohysterectomy in dogs. No side effects were observed, no rescue analgesic was required.

To Cite This Article: Lu D, Yin Y, Wu C and Ma X, 2016. Analgesic effects of lidocaine and fentanyl alone or in combination undergoing ovariohysterectomy in female dogs. Pak Vet J, 36(4): 435-439.

INTRODUCTION

Canine ovariohysterectomy is a common surgical procedure performed in veterinary hospitals. The safe, effective and cost effective analgesia and anesthesia are needed during canine ovariohysterectomy. In order to achieve these goals, multi-modal approaches had been employed by many veterinarians, for the purpose of increasing single agent efficacy with decreased side effect (Stevens *et al*., 2013). Isoflurane (ISO) has been widely used in veterinary medicine, its benefits include a low blood-gas partition coefficient so that it can be convenient control of anesthetic depth. ISO also has a favorable pharmacokinetic profile, which can produce a rapid induction and recovery from anesthesia because of uptaking and eliminating anesthetic gas via the lungs (Gutierrez-Blanco *et al*., 2013). However, animals with systemic diseases will lead to cardiovascular depression if ISO is being used for anesthesia maintenance only. In order to avoid side effects, ISO must be carefully monitored to prevent excessive anesthetic depth.

Canine ovariohysterectomy elicits pain, so adequate analgesia is very important for animal welfare and crucial in reducing adverse effects such as loss of anorexia, self-inflicted injury and so on. (Morgaz *et al*., 2014). For this purpose, analgesics with action mechanisms within a multimodal analgesic protocol are combined, and this combination is common in veterinary medicine (Lamont, 2008, Lu *et al*. 2014). Therefore, the combination of these analgesics may decrease the concentrations of each agent and reduce its side effects (Tobias and Leder, 2011).

Opioids are most commonly administered to dogs because they can provide excellent analgesia during intraoperative period by reducing requirements for other anesthetic agents, and they are also being administrated into the recovery period for managing postoperative pain (Egger *et al*., 2007; Anderson and Day, 2008). Preanesthetic medication is the administration of anesthetic before anesthesia, which is used to prepare the anesthesia and help to reduce of pain and enhance the hypnotic effects of general anesthesia, and reduce the vagal reflexes of intubation (Raszplewicz *et al*., 2013).

Fentanyl is a synthetic μ-opioid receptor agonist which is a short-acting opioid, has been used as analgesic by binding to opioid receptors within the central and peripheral nervous system (Gutierrez-Blanco *et al*., 2015). Local analgesia is another pharmacological option, which can reversibly block the sodium channels of the nerves, prevents noxious stimuli potential propagation along the nerve fiber (Ramsey, 2008). Lidocaine is an amide local anesthetic, which is usually used to provide local anesthesia in veterinary medicine, and can reduce the dosage of opioids required for maintaining analgesia during anesthesia (Zilberstein *et al*., 2008). It also can be used for treating ventricular arrhythmias in dogs (Pariaut *et al*., 2008). Drugs such as fentanyl and lidocaine have been used in an attempt to produce inhalant anesthetic-sparing effects resulting in less cardiovascular depression and good perioperative analgesia in dogs (Columbano *et al*., 2012). However, there is little of information about the efficacy and analgesia effects produced by these analgesics when administered alone or in combination to dogs undergoing ovariohysterectomy (Gutierrez-Blanco *et al*., 2013), but there are a few postoperative analgesia information about these agents used before surgery.

The objective of this study was to evaluate the analgesia effects of fentanyl, lidocaine and the combination of fentanyl-lidocaine in dogs undergoing ovariohysterectomy. The authors hypothesized that fentanyl, lidocaine and their combination would have better anesthesia and analgesia effect than a control group administered saline in dogs during the surgical manipulation.

MATERIALS AND METHODS

Animals: This clinical study protocol was approved by the Institutional Animal Care and Use Committee of Veterinary Medicine at the Northwest A&F University. Forty-eight various breeds intact non-pregnant female dogs were enrolled in a randomized, prospective, blinded clinical study at the Xi'an Teaching hospital of Northwest A&F University for elective ovariohysterectomy. Mean age of dogs was 1.2±0.51 years and mean body weight 12±5.5 kg. Dogs with arrhythmia, obese or other systemic diseases such as diabetes were excluded for this study. Animals had been administrated any anti-inflammatory drugs or analgesic within 15 days before the surgery were also not be used in this study. The dogs were in anestrus and considered to be healthy based on their history, physical examination, routine hematological and plasma biochemical tests prior to the start of the experiment. Food, but not water, was withheld for 12 hours before the study commenced.

Anesthetic and surgical procedure: Animals were randomly divided into three groups (n=16 in each group), drugs and fluids were given by a 20 gauge catheter which was aseptically placed into a cephalic vein, and 3 mL/kg/hour saline (0.9%, Harbin Pharmaceutical Group Company Limited, Harbin, China) was administrated throughout anesthesia.

Dogs were induced with 6 mg/kg propofol (1%, Libang Pharmaceutical Factory Co., Ltd, Xi'an, China), appropriately sized cuffed endotracheal tube was performed, and a non-rebreathing system was connected with these dogs. Anesthesia was maintained with 2% (vaporizer dial setting) isoflurane (2.5%, Jiupai Pharmaceutical Factory Co., Ltd, Shijiazhuang, China), and oxygen flow rates were set at 100 mL/kg/min after intubation and 10 minute later, the oxygen flow was reduced to 50 mL/kg/min. After 15 minutes of induction, animals received 4 mg/kg lidocaine (Cheuk-Fung Pharmaceutical Factory Co., Ltd, Zhengzhou, China) (Group LIDO), or 3 μg/kg fentanyl (Humanwell Pharmaceutical Factory Co., Ltd, Yichang, China) (Group FENT), or 4 mg/kg lidocaine and 3 μg/kg fentanyl (Group COMB) intravenously (IV), and all of them were given within 3 minutes.

Baseline physiologic parameters included heart rhythm (HR), respiratory rhythm (RR), noninvasive systolic, diastolic, and mean arterial blood pressure (SAP, DAP, and MAP) and rectal temperature (RT) were measured by Datex-OhmedaS/5^{TM} monitor (Datex-Ohmeda Division Instrumentarium Corp, Helsinki, Finland) before and after drugs administration, and recorded every five minutes during the period of anesthesia. Arterial blood samples were also obtained from the femoral artery by 2.5mL heparinized syringes, and immediately analyzed for arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial pH, bicarbonate (HCO_3^-). Blood-gas measurements were corrected to body temperature (RAPIDLab®248, Siemens Healthcare Diagnostics Inc., Tarrytown, USA). All dogs experienced a standard midline ovariohysterectomy under general anesthesia by the same surgeon. Another clinician, unaware of the premedication used, monitored anesthesia and assessed the pain scores.

Pain assessments: Subjective pain analyses were performed for the assessment of postoperative pain during the surgery. The pain assessment was performed after the measurement of physiological parameters (HR, RR, blood pressure, RT) at the following time points: T1=before induction, T2=shortly after injection of LIDO, FENT Or LIDO and FENT, T3=at the beginning of the skin incision, T4=immediately after celiotomy, T5=surgical manipulation of the ovaries (immediately after clamping of the ovarian pedicle), T6=at the moment of extubation, T7=one hour after extubation, T8=three hours after extubation and T9=six hours after extubation.

Pain scores were assessed by a composite multidimensional pain scale, based on that of Case *et al*. (2011) and Tsai *et al*. (2013) (Table 2), the categories included comfort, activity, appearance, posture, vocalization, and wound touch. Pain was assessed up to 6 h after extubation. An increase of HR or SAP >15% of the previous moment would be indicative of pain, and ETiso should be increase 0.2%. The animals remained under supervision in postoperative period at T7, T8 and T9. If a dog's total subjective pain score≥8, or its sub-score≥3 in any one category, rescue analgesic with 2 mg/kg IM Tramadol (2 mg/kg, Xudong Haipu Pharmaceutical Factory Co., Ltd, Shanghai, China) was administrated and the dog was excluded from further data analysis in the study. Before discharge from the hospital, dogs received tramadol hydrochloride Injection (IM, bid) (2 mg/kg, Xudong Haipu Pharmaceutical Factory Co., Ltd, Shanghai, China) for 3 days after surgery.

Statistical analysis: Results were reported, and data summarized as median and range. All statistical analyses were performed using SPSS 16.0 (SPSS- Statistical Product and Service Solutions 16.0, SPSS Incorporation, Chicago, Illinois). The Kruskal-Wallis test was used for analyzing pain scores within a group, and Mann-Whitney test was performed among groups within the time points. Descriptive statistics was used for qualitative variables. Continuous data were analyzed by means of ANOVA. Within each group, Dunnett's test was performed to compare all time points with the baseline. Tukey's test was used for analyzing differences between groups within the time points. Values of P<0.05 were defined significant.

RESULTS

Surgery was performed, and no complications were observed in all animals. The duration of anesthesia time ranged from 45 to 65 minutes, and the surgery time was 35 to 50 minutes. No significant differences were found among groups for the duration of anesthesia and surgery.

HR was significantly lower at T4 in FENT, and significantly higher at T6 in FENT, LIDO and COMB treatment (Table 1). Changes in respiratory parameters were significantly increased at T6 in FENT, LIDO and COMB when compared to T1 (Table 1). There were very significant reductions in SAP, DAP and MAP at T3 and T4 when compared with T1 in FENT. However, SAP, DAP and MAP were highest at T6 when compared with baseline in all groups. DAP were significantly decreased at T3 in COMB. DAP and MAP was higher at T5 when compared with T1 in LIDO and COMB (Table 1). SAP, DAP and MAP in LIDO group were significantly higher than FENT group at T5. Rectal temperature significantly decreased in all groups from T3 to T7 in all groups (Table 1).

Subjective pain scores had no differences within groups from T1 to T3. FENT group had lower scores compared with other groups at T4 and T5. LIDO, FENT and COMB had no differences within from T6 to T9. Rescue analgesia was no need during this study. The maximal subjective pain scores were observed at T8 in all groups (Figure 1).

Table 1: Variables (mean±SD) recorded in isoflurane-anaesthetized dogs undergoing ovariohysterectomy receiving an IV injection of 4 mg/kg lidocaine (LIDO), 3 µg/kg fentanyl (FENT) or 4 mg/kg LIDO and 3 µg/kg FENT (COMB) before the surgery

		T1	T2	T3	T4	T5	T6	T7	T8	T9
HR	LIDO	113±10	110±8	103±10	105±7	123±12	135±18*	114±15	115±9	117±11
	FENT	115±10	103±7	95±11	93±15*	110±10	130±11*	110±10	112±12	115±16
	COMB	118±12	107±11	98±7	96±12	120±15	138±12*	120±17	123±15	119±12
RR	LIDO	28±5	34±8	22±5	28±8	39±6	42±9*	23±7	26±6	25±7
	FENT	25±6	29±4	17±4	22±7	32±8	38±10*	24±8	26±4	28±9
	COMB	27±5	33±9	26±5	32±7	37±7	40±9*	27±5	28±7	26±6
SAP	LIDO	117±9	110±10	101±13	104±15	133±17^{a}	150±18*	110±11	113±15	112±12
	FENT	115±8	98±8	85±10*	90±8*	108±9^{b}	138±15*	108±15	111±12	113±11
	COMB	113±7	102±9	94±9	98±10	128±14^{ab}	144±11*	120±9	116±17	115±15
DAP	LIDO	78±7	70±6	63±8	66±9	97±11^{*a}	118±10*	70±8	72±9	70±9
	FENT	75±8	65±7	52±8*	54±10*	78±10^{b}	106±16*	68±9	70±10	68±8
	COMB	77±7	68±8	60±7*	63±8	93±10^{*ab}	110±9*	72±11	75±10	73±11
MAP	LIDO	88±7	85±7	77±10	80±12	110±13^{*a}	126±12*	85±9	87±10	85±12
	FENT	86±8	77±6	65±9*	67±10*	86±9^{b}	115±16*	81±8	85±9	82±11
	COMB	85±7	80±8	72±10	78±11	105±11^{*ab}	122±11*	87±10	89±11	86±9
RT	LIDO	38.8±0.2	38.5±0.1	38.2±0.2*	37.9±0.2*	37.0±0.1*	36.5±0.1*	37.2±0.2*	38.7±0.2	38.9±0.2
	FENT	39.0±0.1	38.6±0.4	38.0±0.3*	37.7±0.2*	36.6±0.2*	36.2±0.1*	37.1±0.1*	38.8±0.3	39.1±0.1
	COMB	38.7±0.1	38.4±0.3	38.1±0.1*	37.6±0.1*	36.8±0.3*	36.3±0.1*	37.2±0.3*	38.8±0.1	38.9±0.2

*Significantly different from baseline values (P<0.05). Different superscripts (a, b) significantly different among groups (P<0.05).

Table 2: Subjective pain score system (based on Case *et al.*, 2011; Tsai *et al.*, 2013)

Observation	Score	Criteria
Comfort	0	Awake or asleep, interested in surroundings
	1	Mild agitated or dissociated of its environment, uninterested in surroundings
	2	Moderate agitated or depressed
	3	Uncomfortable, extremely agitated and restless, it lies down and stands up continuously
Activity	0	Resting or asleep
	1	Awake
	2	Restless (pacing continuously; getting up and down)
	3	Rolling or thrashing
Appearance	0	Submissive
	1	Overtly friendly
	2	Wary
	3	Aggressive
Posture	0	Sleeping or calm
	1	Sternal or sitting up
	2	Standing up with head hanging
	3	Guarded posture and attempt to find a comfortable position
Vocalization	0	Quite
	1	Vocalizing but responds to quite voice and stroking
	2	Intermittent vocalization
	3	Continuous vocalization
Response to palpation	0	Normal, allows palpation of surgical site
	1	Allows but then moves away, tenses or looks when surgical area touched
	2	Increased whining or painful expression when surgical area touched
	3	Will not allow general surgical area to be touched

Pain score was calculated as the sum of scores for the 6 individual categories; possible scores ranged from 0 to 18.

Table 3: Arterial blood variables (mean±SD) recorded in dogs undergoing ovariohysterectomy receiving an IV injection of 4 mg/kg lidocaine (LIDO), 3 μg/kg fentanyl (FENT) or 4 mg/kg LIDO and 3 μg/kg FENT (COMB) before the surgery

		T1	T2	T3	T4	T5	T6	T7	T8	T9
pH	LIDO	7.34±0.03	7.33±0.04	7.31±0.03	7.32±0.07	7.40±0.05	7.26±0.06	7.29±0.07	7.33±0.07	7.35±0.05
	FENT	7.34±0.02	7.32±0.06	7.29±0.05	7.30±0.08	7.35±0.02	7.25±0.03	7.26±0.05	7.32±0.05	7.36±0.08
	COMB	7.33±0.04	7.31±0.07	7.29±0.05	7.30±0.05	7.34±0.06	7.23±0.07	7.28±0.07	7.30±0.06	7.36±0.06
PaO_2	LIDO	98.3±4.5	439.5±84.8*	408.8±72.8*	423.8±75.8*	563.3±87.8*[a]	336.2±76.5*	116.3±13.5	101.3±11.2	96.8±5.4
(mmHg)	FENT	96.8±6.8	403.5±93.7*	378.8±77.3*	390.8±71.3*	450.8±63.8*[ab]	305.3±93.8*	107.3±9.1	94.5±9.8	95.3±6.1
	COMB	99.8±3.8	425.3±75.8*	394.5±71.3*	409.5±92.3*	550.5±102.1*[a]	328.5±90.3*	111.3±12.7	102.2±11.3	98.3±6.7
$PaCO_2$	LIDO	38.6±4.5	36.8±4.2	39.7±3.8	36.7±4.5	36.1±3.8	43.5±4.3	40.5±2.3	39.4±3.6	37.5±4.1
(mmHg)	FENT	38.3±3.8	33.7±6.1	39.2±4.5	36.2±5.3	35.2±6.1	42.1±3.7	39.8±4.2	39.2±3.9	37.7±3.9
	COMB	38.4±3.7	36.7±6.3	39.1±3.3	37.5±4.4	37.5±3.9	44.3±3.8	41.3±1.9	40.5±2.7	37.2±4.7
HCO_3^-	LIDO	22.3±2.1	20.1±2.3	22.7±2.5	21.5±2.1	20.7±2.1	25.1±2.4	23.1±2.2	22.8±2.6	21.9±2.2
(mmol/L)	FENT	22.4±1.9	19.7±2.4	22.6±2.3	21.0±1.9	19.5±2.7	24.3±2.3	22.7±2.6	22.5±2.1	21.3±1.9
	COMB	22.7±2.5	20.5±2.3	22.9±2.6	22.3±2.3	20.1±2.6	25.7±2.8	23.5±1.9	23.1±1.9	22.1±2.3

*Significantly different from baseline values (P<0.05). Different superscripts (a, b) significantly different among groups (P<0.05).

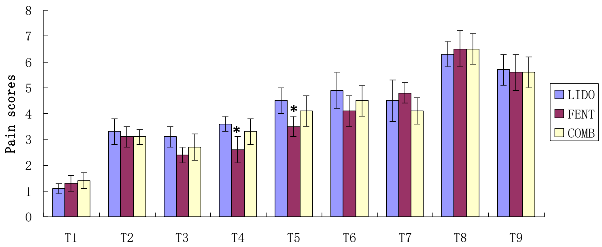

Fig. 1: Pain scores according to subjective pain score system after IV injection of 4 mg/kg lidocaine (LIDO), 3 μg/kg fentanyl (FENT) or 4 mg/kg LIDO and 3 μg/kg FENT (COMB) before the surgery. Results are expressed as mean±SD n=16 for each group. Compared within the different groups at the same time-point, *P<0.05.

pH, $PaCO_2$, PaO_2 and HCO_3^- were not significantly different within groups at Baseline. Some obvious differences were found from T2 to T6 compared with baselines, and FENT were insignificant lower than LIDO at T5 in PaO_2 (Table 3).

DISCUSSION

Ovariohysterectomy is one of the most common surgeries in female dogs, and it usually leads to inflammation and tissue trauma, which can cause pain (Lemke *et al.*, 2002). The adequate analgesia at postoperative period in dogs undergoing ovariohysterectomy is very important for animal welfare and improves postoperative recovery, and also can avoid adverse effects such as anorexia, self-inflicted injury or behavioral alterations. So ovariohysterectomy is a good clinical model in the study of preoperative analgesics (Tsai *et al.*, 2013).

Acevedo-Arcique *et al.* (2014) had reported that constant rate infusion LIDO didn't cause clinically significant changes in HR and blood pressure in dogs which were anaesthetized with isoflurane. Regarding the effects on HR, our recorded data showed that FENT was lower compared with other groups throughout the study. Fentanyl as a short-acting opioid may cause bradycardia by increasing vagal tone (Steagall *et al.*, 2006). In this case, a steady decline of HR were demonstrated in FENT group, and had a significant different with baseline at T4.

In this study, we evaluate the effect of LIDO, FENT and COMB on respiratory system by monitoring RR. Fentanyl is a potent μ-opioid receptor agonist that was discovered to identify an improved dogs' analgesic over morphine during ovariohysterectomy (Aguado *et al.*, 2011), and its major adverse effect is respiratory depression because it has a direct effect on central nerves system respiratory centers, leading to depression of the respiratory system (Steagall *et al.*, 2006). Respiratory depression may be occurred when LIDO was given by intravenous infusion (MacDougall *et al.*, 2009). Our results showed that RR in all treatments were not changed significantly compared with baseline from T2 to T5 may be due to surgery handling, but significantly increased at T6 because of exclude stress. However, the changes in RR remained within clinically acceptable limits in all treatments.

In the present study, we observed significant declines in SAP, DAP and MAP at T3 and T4 in FENT group. Blood pressure increased at T5 could be expected as an evidence of pain from painful stimulus caused by clamping of the ovarian pedicle due to limited analgesic effect of LIDO at this time. Current research had indicated that concurrent administration of fentanyl and isoflurane in dogs resulted in a significant decrease in blood pressure (Keating *et al.*, 2013). And a significant increase of blood pressure in all groups was observed when the tubes were extubated at T6. It is possible that blood pressure is a more sensitive indicator of the noxious stimuli following the surgery than HR, so the higher SAP, DAP and MAP in LIDO and COMB groups compared with FENT group can be explained by the lower blood pressure at T5.

Concerning the RT, these values significantly decreased in all groups from T3, and remain low until T7. This is justified by the losing of thermoregulatory control by isoflurane which causes a depression of the CNS. Further, the fact of the decrease in RT may be due to the muscle relaxation and decrease in metabolic rate.

The results suggest that LIDO and FENT may provide equivalent post-operative analgesic effects in dogs after ovariohysterectomy in this study. Several postoperative pain score systems had been developed for dogs to provide a systemic procedure to determine whether additional pain management is necessary (Devitt *et al.*, 2005). Therefore, a modified composite multidimensional pain scale was used in this study to assess subjective pain scores. Lidocaine can block sodium channel that produces local analgesia by inhibition of excitability of the cell (Brinkrolf and Hahnenkamp, 2014). Fentanyl commonly used as intraoperative analgesics since they induced profound analgesia. There are a lot of clinical reports in dogs which indicated LIDO and FEND residual analgesic effects in the postoperative period after administration during ovariohysterectomy (Morgaz *et al.*, 2008; Tsai *et al.*, 2013).

Values regarding blood gas did not differ between groups at any of the time-points, indicating absence of respiratory depression induced by LIDO, FENT and COMB. When appropriate doses LIDO and FENT are used in healthy dogs via intravenous infusion, the acid-base balance is maintained within the normal parameters (Gutierrez-Blanco *et al*., 2013). However, this study had shown that PaO_2 was higher in all groups from T2 to T6 compared to T1, and statistically significant were found during these time-points. Obviously, the results were disguised because all dogs in all groups during these time-points were submitted to isoflurane with 100% oxygen. In addition, it was shown that the pH and $PaCO_2$ were almost decreased during these time-points, which also occurred due to the respiratory depression by isoflurane (Escobar *et al*., 2011) and the $PaCO_2$ were higher at T6 owing to extubation stimuli.

In conclusion, this study demonstrated that, at the doses of administration via intravenous infusion, LIDO and FENT as well as their combination resulted in greater analgesia effect during ovariohysterectomy in dogs. And all of three protocols could provide minimal overall effect on the cardiopulmonary function and keep acid-base balance within clinically acceptable limits.

Author's contribution : Lu DZ and Ma XW designed experiments; Lu DZ, Yin YP and Wu CC carried out experiments; Lu DZ analyzed experimental results and wrote the manuscript; Ma XW revised the Manuscript. All authors interpreted the data, critically revised the manuscript for important intellectual contents and approved the final version.

Acknowledgment: This study was supported by the Fundamental Research Funds for the Central Universities (Grant No. 2452016039), Foundation for Talent of Northwest A&F University (Grant No. Z109021110), and National Natural Science Foundation of China (Grant No. 31301970 and 31302153).

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