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Clinical evaluation of multimodal analgesia for optimum post-operative pain management in dogs undergoing ovariohysterectomy

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Abstract
The present study was conducted for clinical evaluation of different multimodal analgesia protocols for optimum post-operative pain management in 12 clinical cases of isoflurane anaesthetized dogs undergoing ovariohysterectomy. These dogs were randomly divided into two equal groups in which Group A received fentanyl, lignocaine and ketamine (FLK) CRI and Group B received buprenorphine, lignocaine and ketamine (BLK) CRI throughout the surgery, along with administration of carprofen before surgery as well as 24 and 48 hours after recovery. Quality of anaesthesia was satisfactory in both the groups. Extubation and recovery time was longer in group B along with mild sedation effect at recovery, while recovery was smooth in Group A. Isoflurane-sparing effect was greater in Group A as compared to Group B. The mean values of rectal temperature, heart rate and respiration rate at various intervals exhibited a significant decreasing trend in both the groups, but were within the normal physiological limit. The arterial blood pressure and SpO_2 values of both the groups fluctuated significantly throughout the anaesthesia period and hemodynamic stability was well maintained in both the groups. The short form of Glasgow composite measure pain scale (GCMPS-SF) exhibited non-significant variation of pain in between the groups and both the groups showed decreasing pain scores upto 72 hours of surgery. No dog in any group required rescue analgesia. On the basis of observations, administration of FLK CRI and carprofen as multimodal analgesic along with isoflurane anaesthesia provided optimum analgesic effect than BLK CRI and carprofen for post-operative pain management in dogs undergoing ovariohysterectomy.

Keywords: fentanyl, buprenorphine, ketamine, lignocaine, CRI, dog, multimodal

Introduction
Pain is an extremely complex multidimensional experience comprising both sensory and affective (emotional) elements accompanying potential or actual tissue damage (Tranquilli *et al.*, 2007) [1]. In a clinical setting, analgesia may be induced by obtunding or interrupting the nociceptive process at one or more points between the peripheral nociceptor and the cerebral cortex. This can be achieved by using analgesic drugs of different pharmacologic mechanism such as NSAIDS, α2-agonist, local anaesthetics, opioids as balanced or multimodal analgesics administered through various routes because it provides drug synergism, improved efficacy, facilitate pain treatment and minimize adverse autonomic nervous system reflexes. Constant infusion (CRI) of drugs prevents the undesirable effects produced by the peaks and valleys of intermittent bolus administration and maintains a constant plasma concentration of the drug. Infusion of multimodal analgesic drug combinations is also advantageous as it reduces the amount of inhalant anesthetic required for maintaining general anesthesia (also known as Partial Intravenous anaesthesia-PIVA) and thereby lowers the risk of cardiorespiratory depression. Nowadays, the combination of opioids along with ketamine and lignocaine are commonly being used in veterinary practice for management of pain. Opioids reduce the transmission of nociceptive signal by binding with the μ and κ opioid receptors. Lignocaine acts by blocking the sodium channels present in sensory nerve fibers, thereby inhibiting electric impulse conduction; its perioperative administration produces analgesic and antiarrhythmic effects. Ketamine acts as a non-competitive NMDA receptor antagonist and prevents wind-up and central sensitization and has been found to produce analgesia peri and postoperatively with low infusion doses (Muir *et al.*, 2003) [2].

Methodology
The present study was conducted on 12 healthy clinical cases of female dogs that were presented for elective ovariohysterectomy at TVCC, PGIVAS, Akola. The dogs underwent thorough clinical examination before including them into the study. All the dogs were randomly divided into two equal groups (n=6) viz., Group A and Group B irrespective of their breed, age and body weight.

Preparation and premedication of animals
All the dogs were fasted for 12 hours and water was withheld for 6 hours prior to the procedure. The dogs were sedated using Inj. Xylazine @ 1 mg/kg b.wt. intramuscularly. Premedication was done using Inj. amoxicillin & cloxacilin @ 10mg/kg b.wt., Inj. Chlorphenaramine maleate @0.4mg/kg b.wt. intramuscularly and Inj. carprofen @ 4mg/kg b.wt subcutaneously prior to induction of anaesthesia, and at 24h and 48h post recovery from anaesthesia.
Catheterization of the cephalic vein was done using intravenous catheter for administration of the analgesic drugs CRI. The abdomen was clipped, shaved and scrubbed with antiseptic povidine iodine solution for aseptic preparation for surgery.

Anaesthetic protocol
The dogs of both the groups received Inj. propofol @ 4mg/kg b.wt. IV for induction of anaesthesia and maintenance was carried out using isoflurane @ 1.5% MAC given in 100% oxygen through a closed rebreathing circuit.

Analgesic Protocol
The analgesic CRI was prepared by adding commercially available fentanyl @ 0.0036mg/kg/hr or buprenorphine @ 0.0030mg/kg/hr, lignocaine @ 3mg/kg/hr and ketamine @ 0.60mg/kg/hr to 0.9% normal saline solution bottle so as to make a 250ml solution. This was done by replacing an equal volume of the normal saline solution with those of the total added analgesic solutions.

Group A (n=6): FLK CRI
Loading dose: Inj. fentanyl @ 0.003mg/kg b.wt, Inj. lignocaine @ 1mg/kg b.wt. and Inj. ketamine @ 0.25mg/kg b.wt. intravenously 5-10 min after induction.
Maintenance dose: Fentanyl @ 0.0036mg/kg/hr, lignocaine @ 3mg/kg/hr and ketamine @ 0.60mg/kg/hr following loading dose.

Group B (n=6): BLK CRI
Loading dose: Inj. buprenorphine @ 0.015mg/kg b.wt, Inj. lignocaine @ 1mg/kg b.wt. and Inj. ketamine @ 0.25mg/kg b.wt. intravenously 5-10 min after induction.
Maintenance dose: Buprenorphine @ 0.0030mg/kg/hr, lignocaine @ 3mg/kg/hr and ketamine @ 0.60mg/kg/hr following loading dose.
The continuous rate infusion in both the groups was carried out using fluid bag of 250 ml and micro drip infusion set having precision setting of ml/hr and maintained throughout the surgery at a flow rate of 3ml/kg/hr.

Parameters studied
Assessment of anaesthesia was done by evaluating quality of anaesthesia based on various reflexes, extubation time and recovery time. Isoflurane concentration required for maintenance was evaluated on the basis of surgical depth exhibited by the dogs (response to different pain stimulus or MAP value) and recorded at the end of the procedure. Clinico-physiological and hemodynamic parameters were recorded at 0 min (after sedation), 15 min (after loading dose), 30, 45, 60, 75, 90, 105, 120 and 24h, 48h and 72h after recovery. Pain assessment was done using using the Short Form of Glasgow Composite Measure Pain Scale (SF-GCMPS). The pain scores were recorded just after recovery of the animal from anaesthesia at 0h, then after 1h, 2h, 3h, 4h, 24h, 48h and 72h.

Statistical analysis
The data obtained during the recording of the parameters were statistically analysed in a two-way factorial design by Analysis of Variance (ANOVA) using WASP 2.0 and SPSS 21.0 programs. For non-parametric data (Pain scores), Kruskal-Wallis H test (rank based test) was carried out.

Result and Discussion
Assessment of anaesthesia
Assessment of anaesthesia was done by evaluating the quality of anaesthesia and analgesia following administration of the two analgesic protocols as well as extubation time, recovery quality and time. Quality of anaesthesia was satisfactory in both the groups, where pedal and palpebral reflex were completely abolished after 30 min of observation, eyeballs were ventro-medially located and no pain on stimulus exhibited in both the groups. Jaw tone completely abolished in group B and moderately up to 45 min to complete in the later intervals in group A (Rashmi, 2017) [3]. The mean time required for extubation and recovery from anaesthesia was significantly longer in group B (19.83±1.01; 33.83±1.13 min) as compared to group A (11.50±1.76; 19.16±1.53 min). This can be attributed to the administration of buprenorphine as it has longer half-life than fentanyl and also produces sedation effect post administration (Barbarossa *et al*., 2017) [4]. Recovery was smooth and rapid with no vocalization in group A whereas mild sedation, lameness was seen in group B up to 1hr post extubation where dogs took few attempts to stand (Velazquez-Delgado *et al*., 2021) [5].

Table 1: Mean ± SE values of Extubation time (Minutes) and Recovery Time (Minutes) of both the groups

Group	Extubation Time (Minutes)	Recovery Time (Minutes)
Group-A	11.50±1.76^{a}	19.16±1.53^{a}
Group-B	19.83±1.01^{b}	33.83±1.13^{b}

Means bearing different superscript are significant at 1% level of significance (P<0.01)

Isoflurane concentration
The mean concentration of isoflurane required by animals in both the groups for maintenance was estimated on the basis of pain stimulus exhibited by each animal during surgery and was recorded by the end of the anaesthetic procedure. The mean value and % reduction of isoflurane required in group A was 0.83 ± 0.04 (44.60%) which was significantly lower than isoflurane required in group B i.e. 1.03 ± 0.05 (31.33%). The maintenance of both the groups was initiated with 1.5% isoflurane concentration at the start of the protocol. Reduction

in isoflurane concentration in both the groups might be attributed to the administration of opioids, ketamine and lignocaine. Opioid usually binds with the μ and κ opioid receptors Lignocaine blocks the sodium channels present in sensory nerve fibers, thus preventing electric impulse conduction Ketamine prevents central sensitization by acting as non-competitive NMDA receptor antagonist. The combination of the three drugs produces synergistic effect and effectively reduces isoflurane concentration peri-operatively in a dose-dependent fashion along with maintenance of hemodynamic stability. The lesser reduction in group B might be due to the delayed onset of action of buprenorphine (40-60 min) as compared to the fast action (2-5 min) of fentanyl (Muir *et al*., 2003, Steagall *et al*., 2006, Columbano *et al*., 2012) [2, 6, 7].

Table 2: Mean ± SE values of Isoflurane concentration (%) of both groups

Group	Isoflurane concentration (%)
Group-A	0.83 ± 0.04^{a}
Group-B	1.03 ± 0.05^{b}

Means bearing different superscript are significant at 5% level of significance (P<0.05)

Clinico-physiological parameters

Rectal temperature of both the groups did not differ significantly. The pooled mean values of both the groups at different intervals showed a significant decreasing trend from sedation (101.55±0.04) up to 120 min of anaesthesia (99.3±0.08). The decline in rectal temperature in both the groups might be due to the administration of different anaesthetic and analgesic drugs that produce hypothermia by causing thermoregulatory depression and decrease in metabolic rate (Rashmi, 2017, Watanabe *et al*., 2018 and Yohannes, 2018) [3, 8, 9]. Ketamine causes alteration in vasomotor tone and decrease in body heat redistribution (Chaung *et al*., 2020) [10]. Opioids causes decrease in heat production from the body by lowering the temperature set point which in turn induces panting for increasing heat loss in dogs (Anam, 2018) [11].

The mean values of respiratory rate in group B exhibited slightly non-significant higher values than group A. The pooled mean values of respiratory rate of both the groups at different intervals showed a significant decreasing trend from sedation (15.33±0.16) up to 90 min (9.25±0.25) and then increased significantly at 120 min of anaesthesia (10.91±0.08). The respiratory depression observed after sedation up to 105 minutes of anaesthesia might be attributed to the various drugs used in the experiment viz., xylazine, propofol and ketamine which produces depression at the respiratory centre and isoflurane which causes dose-dependent increase in $PaCO_2$ (Steffy and Howland, 1997 and Yohannes, 2018) [12, 9]. The depression might mainly be due to the administration of opioids which resets the CO_2 threshold in the respiratory centre present in the brainstem (Anam, 2018) [11].

The mean values of heart rate in group B (80.9±2.1) exhibited significantly higher values than group A (79.38±1.94). The pooled mean values of heart rate of both the groups increased significantly from sedation (77.5±0.6) to 15 min (86±0.16), which then showed a significant decreasing trend up to 105 min of anaesthesia (69.83±1.33). The declining trend observed in both the groups might be attributed to the increase in vagal tone and systemic vascular resistance which leads to bradycardia mediated by barorecepters as a result of opioid administration (Zhang *et al*., 2016, Watanabe *et al*., 2018) [13, 8].

The cardiopulmonary stability was well maintained and the altered values of all the parameters returned towards the normal non-anaesthetic values after 24 hours of observation.

Table 3: Mean ± SE of Rectal temperature (^{0}F) of both the groups

Time Interval (min/hours)	Group-A	Group-B	Pooled Mean
0	101.51±0.35	101.6±0.23	101.55±0.04^{g}
15	101.26±0.29	101.18±0.24	101.22±0.04^{fg}
30	101.05±0.31	101.16±0.21	101.1±0.05^{ef}
45	100.76±0.3	100.68±0.16	100.72±0.04^{de}
60	100.75±0.29	100.65±0.2	100.7±0.05^{d}
75	100.35±0.19	100.16±0.24	100.25±0.09^{c}
90	99.96±0.13	99.81±0.37	99.89±0.07^{bc}
105	99.93±0.21	99.63±0.22	99.78±0.15^{b}
120	99.38±0.15	99.21±0.19	99.3±0.08^{a}
24hr	101.2±0.28	101.4±0.22	101.3±0.1^{fg}
48hr	101.56±0.33	101.18±0.23	101.37±0.19^{fg}
72hr	101.41±0.11	101.4±0.17	101.4^{fg}
Pooled mean	100.76±0.14	100.67±0.16	

Means bearing different superscripts differ significantly (5% level of significance)

Table 4: Mean ± SE of respiration rate (breaths per min.) and heart rate(beats per min.) of both the groups

Time Interval (min/hrs)	Respiration Rate		Pooled Mean	Heart Rate		Pooled Mean
	A	B		A	B	
0	15.16±0.79	15.5±1.11	15.33±0.16^{f}	76.83±2.72	78.16±2.32	77.5±0.6^{d}
15	13.16±0.79	13.83±1.01	13.5±0.33^{e}	85.83±2.62	86.16±2.9	86±0.16^{g}
30	11.5±0.61	12.5±0.99	12±0.5^{de}	81.5±3.85	82.33±2.65	81.91±0.41^{f}
45	10.83±0.87	11.16±0.87	11±0.16^{bcde}	78.83±2.25	80.16±2.44	79.5±0.66^{def}
60	9.33±0.42	10.83±0.7	10.08±0.75^{abc}	77.16±2	78.16±2.44	77.66±0.5^{de}
75	9.16±0.47	10.66±0.95	9.91±0.75^{ab}	73.16±1.55	74±2.87	73.58±0.41^{c}

90	9±0.63	9.5±0.71	9.25±0.25^{a}	69.83±1.7	73.5±2.1	71.66±1.83^{abc}
105	10.16±0.79	10.33±0.8	10.25±0.08^{abc}	68.5±1.94	71.16±3.11	69.83±1.33^{a}
120	10.83±0.87	11±0.77	10.91±0.08^{bcd}	69±2.67	71.83±3.26	70.41±1.41^{ab}
24hr	20.33±1.42	20±1.15	20.16±0.16^{g}	91±1.39	92.66±1.35	91.83±0.83^{h}
48hr	20.5±1.38	19.83±0.87	20.16±0.33^{g}	90.16±2.35	91.16±2	90.66±0.5^{h}
72hr	20.66±0.84	20.5±0.56	20.58±0.08^{g}	90.83±1.9	91.5±1.56	91.16±0.33^{h}
Pooled mean	13.38±0.49	13.8±0.76		79.38±1.94^{I}	80.9±2.1^{II}	

Means bearing different superscripts differ significantly (5% level of significance)

Haemodynamic parameters

The mean values of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) and SpO_2 varied non-significantly among both the groups. The pooled mean values of SAP and MAP showed significant variations after sedation (0 min) at 30 and 90 min of observation, the DAP values varied significantly after sedation (0 min) at 30 min and between 90 and 120 min of observation. The initial slight decrease in the mean values of blood pressure of both the groups might be due to the action of xylazine and propofol which causes transient depression of myocardial contractility. The decrease might further be due to ketamine, lignocaine, isoflurane and opioids which cause vasodilation leading to fall in BP (Zhang *et al*., 2016, Watanabe *et al*., 2018) [13, 8]. Although the isoflurane concentration requirement reduced subsequently during the procedure, only a slight increase in values was observed attributing it to fentanyl-induced bradycardia that blunted the BP improvement (Steagall *et al*., 2006) [6].

The pooled mean values of SpO_2 was lower after sedation (0 min) which showed a significant ($P<0.01$) increase at 30 min and 45 min of observation, attributing it to the administration of xylazine and other anaesthetic drugs which may cause reduction in peripheral oxygenation and tissue perfusion because of the depression of the ventilation of lungs (Munif *et al*., 2020) [14], after which the values fluctuated at all the intervals of the study. The subsequent increase and maintenance of the values may be due to supplementation of 100% oxygen along with isoflurane during maintenance of anaesthesia (Watanabe *et al*., 2018, Velazquez-Delgado *et al*., 2021) [8, 5].

The haemodynamic stability was well maintained and the altered values of all the parameters returned towards the normal non-anaesthetic values after 24 hours of observation.

Table 5: Mean ± SE of SAP (mmHg) and DAP (mmHg)

Time Interval (min/hrs)	Systolic Arterial Pressure		Pooled Mean	Diastolic Arterial Pressure		Pooled Mean
	A	B		A	B	
0	106±4.51	105±4.39	105.5±0.5^{bcdef}	72.83±1.64	73.66±2.02	73.25±0.41^{defg}
15	101.5±4.07	101.66±4.16	101.58±0.08^{abcd}	67.16±1.79	68.5±3.76	67.83±0.66^{abcd}
30	90.5±5.28	102.836.5	96.66±6.16^{a}	61.5±2.75	69.83±4.46	65.66±4.16^{ab}
45	94.16±6.9	106.66±5.25	100.41±6.25^{abc}	63.5±3.48	72.66±3.37	68.08±4.58^{abcde}
60	96±7.77	99.33±5.55	97.66±1.66^{ab}	65.66±3.29	66.83±3.44	66.25±0.58^{abc}
75	107.33±6.87	103.16±7.23	105.25±2.08^{abcde}	67.33±4.8	69.5±3.38	68.41±1.08^{abcdef}
90	109.5±5.77	111.83±6.27	110.66±1.16^{defgh}	69.16±3.4	71.83±5.21	70.5±1.33^{bcdefg}
105	106±4.3	110.66±3.86	108.33±2.33^{cdefgh}	65±4.06	67.5±2.26	66.25±1.25^{abc}
120	103.5±5.32	108.5±4.66	106±2.5^{bcdefg}	62.83±4.01	63.83±3.17	63.33±0.5^{a}
24hr	128±5.61	128.5±2.74	128.25±0.25^{i}	74.66±2.77	76.5±2.89	75.58±0.91^{g}
48hr	132.66±3.85	126.5±3.92	129.58±3.08^{i}	75±3.93	75.5±2.18	75.25±0.25^{g}
72hr	130.66±2.29	127.16±2.82	128.91±1.75^{i}	76.33±3.86	76.16±2.7	76.25±0.08^{g}
Pooled mean	108.81±3.82	110.98±2.88		68.41±1.40	71.02±1.65	

Means bearing different superscripts differ significantly (5% level of significance)

Table 6: Mean ± SE of MAP (mmHg) and SpO_2 (%)

Time Interval (min/hrs)	Mean Arterial Pressure		Pooled Mean	SpO_2		Pooled Mean
	A	B		A	B	
0	83.83±1.66	84.16±2.25	84±0.16^{defgh}	95.5±0.42	94.83±0.6	95.16±0.33^{a}
15	78.66±2.01	79.50±3.07	79.08±0.41^{abcde}	96.66±0.49	95.33±0.66	96±0.66^{ab}
30	71.16±1.81	80.83±4.82	76±4.83^{a}	97.5±0.61	97±0.57	97.25±0.25^{cd}
45	73.66±4.11	84.16±3.15	78.91±5.25^{abcd}	98.16±0.47	98.5±0.42	98.33±0.16^{efg}
60	75.66±4.02	77.66±3.64	76.66±1^{ab}	97.66±0.66	98.33±0.76	98±0.33^{cdef}
75	80.5±3.77	80.83±4.4	80.66±0.16^{abcdef}	97.83±0.47	96.16±0.83	97±0.83^{bc}
90	82.66±2.97	85±5.46	83.83±1.16^{defgh}	97.16±0.94	97.66±0.42	97.41±0.25^{cde}
105	79.66±3.57	82±2.03	80.83±1.16^{abcdefg}	98±0.77	98.5±0.67	98.25±0.25^{defg}
120	76.33±3.59	78.66±2.99	77.5±1.16^{abc}	98.16±0.3	99±0.36	98.58±0.41^{fg}
24hr	92.66±2.38	93.83±2.54	93.25±0.58^{i}	98.33±0.33	98±0.36	98.16±0.16^{defg}
48hr	94±2.01	92.33±2.18	93.16±0.83^{i}	97.83±0.4	99±0.51	98.41±0.58^{efg}
72hr	94.5±2.4	93.16±2.22	93.83±0.66^{i}	99±0.36	99.16±0.4	99.08±0.08^{g}
Pooled mean	81.94±1.75	84.34±1.91		97.65±0.22	97.62±0.17	

Means bearing different superscripts differ significantly (5% level of significance)

Assessment of pain

Pain scores were recorded just after recovery using GCMPS-SF. The dogs in both the groups exhibited pain when pressure was applied around the surgical site up to 2-3 hours post-extubation but was not observed after 24 hours. Some animals in group B were lame, slow or little reluctant to walk up to 1

hour of recovery due to the sedation effect observed. The pooled mean ranks of both the groups at different intervals exhibited a decreasing trend i.e. 79.12 at 0 hour to 17.5 at 72 hour after recovery. The mean ranks of group B was non-significantly (P>0.05) higher that group A up to 4 hours of observation and subsequently they were equivalent to each other. The administration of lignocaine and ketamine along with fentanyl might have provided synergistic effect and residual analgesia, thus extending the analgesic effect of short-acting fentanyl administered via infusion resulting in lower ranks while slightly higher ranks in group B might be due to the late onset of action of buprenorphine (Gutierrez-Blanco *et al*., 2015) [15]. No significant variation was seen in pooled mean ranks of group A and group B which might be due to the action of carprofen having anti-inflammatory properties and provides analgesia up to 18-20 hours after ovariohysterectomy in dogs (Shih *et al*., 2008) [16]. No dog required rescue analgesia at any time point (Anam, 2018, Velazquez-Delgado *et al*., 2021) [11, 5].

Table 7: Mean ranks of pain scores in both the groups

Interval (hours)	Group 1	Group 2	Pooled mean
0	78.25	80	79.12
1	75.5	81	78.25
2	65	66.66	65.83
3	57.83	50.25	54.04
4	38.66	43.83	41.25
24	33.5	33.6	33.55
48	17.83	17.92	17.87
72	17.5	17.5	17.5
Pooled mean	48.01	48.84	

Conclusions

The infusion of fentanyl along with lignocaine and ketamine administered during maintenance provides better quality and smooth recovery from anaesthesia as well as provides good hemodynamic stability at the doses used in the study. Similarly, the infusion of buprenorphine along with lignocaine and ketamine provides acceptable recovery from anaesthesia along with good hemodynamic stability at the doses used in the study. Fentanyl is found to provide better isoflurane sparing effect than buprenorphine in the study. It can be concluded that administration of FLK CRI and carprofen as multimodal analgesic along with isoflurane anaesthesia provides optimum analgesic effect than BLK CRI and carprofen for post-operative pain management in dogs undergoing ovariohysterectomy.

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