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Effect of propofol vs ketofol on cardiorespiratory functions during ovariohysterectomy in healthy dogs

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Abstract
Background: Ovariohysterectomy involves excision of ovaries and uterus in female dogs. It is a surgical procedure under general anaesthesia. Smooth induction of anaesthesia and recovery after surgery is still a cumbersome process in pets. Propofol is the most commonly used induction agent however, it has depressant effect on respiratory and cardiovascular system. Whereas, ketamine has stimulatory effect on these systems. Therefore, it was hypothesised that the propofol+ketamine combination my improve safety of general anaesthesia in dogs.
Methods: Twelve bitches were divided into two groups and were injected with pre-anaethestic (Butorphanol @ 0.2mg/kg, Acepromazine @ 0.05 mg/kg, & Atropine sulphate @ 0.02mg/kg BW) intramuscularly. Propofol alone (@ 4mg/kg BW) or ketofol 1:1 (propofol @ 2mg/kg + ketamine @ 2mg/kg BW) was injected intravenously after 15 min of pre-anaesthetic administration for induction of anaesthesia. The comparison between the drugs was done by employing statistical analysis techniques which were based on cardiorespiratory parameters, induction and recovery time following drug treatment.
Results: Systolic arterial pressure remains comparatively on higher side in ketofol group than the propofol group. Diastolic arterial pressure was maintained significantly on higher level differ at 30 min & 60 min within the ketofol group. The less isoflurane percentage required for maintaince of anaesthesia in the ketofol group than the propofol group. Respiration rate was more stable and non-fluctuating in the ketofol group, which significant differ from propofol group at post induction. Similarly, heart rate was maintained on higher side with significant difference noted following induction of anaesthesia and during surgery in ketofol group. Oxygen saturation and End tidal carbon dioxide remains stable in both groups with non-significant alteration.

Keywords: Ovariohysterectomy, propofol, ketofol, induction agent, isoflurane concentration, SAP, DAP, MAP

Introduction
Ovariohysterectomy is a surgical procedure that involves excision of both the ovaries and the uterus in female dogs**.** Ovariohysterectomy is perhaps the most widely used surgical technique. In female dogs ailing from reproductive-related difficulties such as pyometra, uterine neoplasia, and other pathological disorders such as metritis, mastitis, or endometritis. Several pet owners find it challenging to manage the reproductive cycle in female dogs, and estrus-related issues such as pro-estrus bleeding, sero-sanguineous discharge, vaginal prolapse, restlessness, and unwanted or undesirable mating. Moreover following the heat cycle, the hormonal swings that induce false conception, are also eliminated using this technique. Neutered dogs if they spayed before their maiden heat have a very low probability of developing mammary cancer. Spaying also eliminate chance of uterine and ovarian neoplasia. Spayed canines tend to live longer than non-spayed.
Ovariohysterectomy is performed under general anaesthesia. The selection of anaesthetic drugs based on the physiological condition and clinical findings to implement safe anaesthesia. General anaesthesia consist of three components, pre-anaesthetic, induction of anaesthesia and maintaince of anaesthesia. Pre-anaesthestic drugs are important and use of pre-anaesthetic reducing dose of induction agent atropine helps to reduce salivary flow and bronical discharge during surgery, acepromazine provide sedation and antiemetic in animals. Butorphanol is commonly used analgesic and anaesthetic adjuvants and have antitussive, antiemetic property.
Propofol is 2, 6-diisopropylphenol that blocks GABA receptor neurotransmission. Propofol is a popular induction drug in dogs because it has a faster induction & smooth

induction, recuperation, quick titration, rapid clearance (Tsai *et al*., 2007) [30]. No anaesthetic drug is considered safe every anaesthetic drug have its own merit and demerits. Therefore, combination of anaesthetic drugs are used to minimise the negative effects of each other this is called balanced anaesthetic approach. Propofol is inadequate as a solitary drug for total intravenous anaesthesia (TIVA) due to its low analgesic properties (Jena *et al*., 2014) [12].

Propofol has a narrow therapeutic range and is associated with a risk of cardiovascular collapse, although it is a safe and effective sedative. Therefore, to minimise dose-dependent respiratory and cardiovascular, as well as hypotension, are the most common effects of propofol (Kennedy & Lesley, 2014). It can be combined with ketamine the ketamine has stimulatory effect on respiration and cardiovascular system.

Ketamine is a dissociation anaesthetic, as it prevents ascending transmission to conscious and unconscious processes from areas of the brain. Ketamine is a non-competitive, phencyclidine hydrochloride N-methyl D-aspartate receptor antagonist (NMDA). It interacts with mu, sigma, kappa, muscarin, and calcium, and opium receptors (Sarton *et al*., 2001) [26]. The benefits of ketamine include heart stability, breathing preservation and analgesic characteristics (Aouad *et al*., 2008) [4].

Combination of ketamine and propofol offers many benefits over the individual drugs which include, limited occurrence of propofol-induced respiratory distress, the supply of analgesia due to ketamine and less cardiorespiratory adverse effects (Mair *et al*., 2009) [17].

Literature available on comparative efficacy of propofol alone and its combination with ketamine as induction of anaesthesia is scanty. Therefore, present study was planned to evaluate

1. To clinically evaluate intravenous propofol alone or in combination with ketamine to induce anaesthesia in healthy and pyometritic bitches.
2. To evaluate anaesthetic effects of propofol and ketamine anaesthesia on haemato-biochemical changes during ovariohysterectomy in pyometritic bitches.

Material and Methods

The study was conducted from January to June 2021 in Department of Veterinary Gynaecology and Obstetrics, and Teaching Veterinary Clinical Complex, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana.

Female Dogs presented for neutering was taken in study with the consent of the owner. Body weight of dogs used for study ranged from 6 to 30 kgs and age ranged from 1 to 4 years. All the dogs were subjected to clinical and hemato-biochemical examination before undertaking ovariohysterectomy operation. Dogs were fastedfor food & water for at least 12 hours before anaesthetic administration. All female dogs were injected with pre-anaesthetic agent's butorphanol at dose rate of 0.2 mg/kg body weight, acepromazine @ 0.05 mg/kg body weight and atropine sulphate @ 0.02 mg/kg body weight intramuscularly. Then the female dogs were randomly allocated into two groups' propofol and ketofol having six dogs in each. Following 15 minutes of pre-anaesthetic administration of induction agent was administrated follows.

Group 1 (Propofol group)

Six female dogs were injected with propofol at the dose rate of 4 mg/kg intravenously. The drug was administered upto till relaxing of jaw or intubation. The maintaince of anaesthesia was done with isoflurane.

Group 2

Six female dogs injected with ketofol (combination of propofol + ketamine), each with dose rate of 2 mg/kg body weight in single syringe intravenously. The drug was administered upto till relaxing of jaw or intubation. Anaesthesia was maintained with isoflurane.

Observations

The evaluation of anaesthetic agents was done on the basis of different parameter like induction time, recovery time and isoflurane concentration required during general anaesthesia along with other cardiorespiratory parameters like heart rate, respiration rate, rectal temperature, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, oxygen saturation and end tidal carbon dioxide.

Heart rate, respiration rate and rectal temperature was recorded before pre-anaesthetic, after pre-anaesthetic, post induction (0 min), 15, 30, 45, 60, 75 and 90 minutes time interval by manually and by multi para monitor. Rest of the parameters were recorded post induction (0 min), 15, 30, 45, 60, 75 and 90 minutes time interval with the help of Multi para monitor.

Statistical analysis was done with the help of Graph Pad 8.0.2 software. Statistical tests used were one way ANOVA post hoc Tukeys test and t- test.

Result and Discussion

Result of the present study showed that induction time did not differ between the dogs administered propofol and ketofol as induction agent. The recovery time (time of extubation) was comparatively faster in the ketofol group than the propofol in present study. Recovery was smooth without any complication like struggling, crying in both the groups.

The use of isoflurane concentration was less in ketofol group this could be the reason for faster recovery. The overall mean of isoflurane concentration for propofol and ketofol was 2.5% and 1.6% respectively. Similar findings with report to requirement of isoflurane had been reported (Bhave *et al*., 2019) [8]. Solano *et al*. (2006) [28] also reported that ketamine appreciably diminished the concentration of isoflurane in anaesthetized dogs.

Table 1: Mean ± SE values of propofol vs ketofol for Induction time (seconds) and Recovery time (min) in elective ovariohysterectomy

Groups	Induction Time (seconds)	Recovery Time (minutes)
Propofol	50.50±3.87	16.10±1.27
Ketofol	49.3.3±3.75	14.79±2.54

Results of present study for different parameters showed in tables 1, 2, 3, & 4

Heart rate did not differ significantly within groups over the period, however, heart rate was significantly higher at induction (0 min) and at 15 min interval in the ketofol group compared to the propofol group. Higher heart rate in ketofol group than propofol group could be due to stimulatory effect of ketamine on cardiac system or due to reduction in propofol dose. The heart rate was maintained comparatively on higher side in ketofol group than the propofol group but remains within normal physiological range for both groups. Similar results had been reported by Bayan *et al*. (2014) [6]; Lee *et al*. (2017) [16].

Significant drop was observed in respiration rate within for both the groups in present study post induction of anaesthesia. The decline in respiration rate was higher in propofol group as

compared to ketofol. When intergroup comparison was done, significant difference was observed at post induction (0 min), 60, 75 and 90 minute time intervals. Propofol caused transient apnea alongwith respiratory depression (Kurun *et al*., 2013) [15]. Ketofol has been reported to cause minimal or absolute no ventilatory depression in both humans as well as cats (Morse *et al*., 2003; Ravasio *et al*., 2012) [19, 22]. Similar effect of ketofol on respiration rate to the present study had been reported by Andolfatto *et al*. (2012) & Bhave *et al*. (2019) [8].

Rectal temperature showing decreasing trend throughout the duration of anaesthesia/surgery in both the groups. Significant difference was found after induction (0min) at 15, 30, 45, 60, 75 and 90 minute time interval from baseline in both groups. When intergroup comparison was carried out, significant difference was noted at 15, 30, 75 and 90 minute time interval between the propofol and ketofol group.

Hypothermia, is produced by combination of sedatives and anaesthetics due to depression of the thermoregulatory center, decreased basal metabolic rate and muscle activity, and depression of peripheral circulation and vasodilation, may be responsible for the decrease in rectal temperature in both groups (Njoku, 2015) [20]. Another investigation also indicated a similar trend in rectal temperature after propofol induction (Bhat, 2015) [7].

Systolic arterial pressure was maintained at higher level in ketofol group. However, when intergroup comparison was made no significant difference was found. In both groups, SAP remained within normal physiological range throughout study period.

The findings from present study corroborated the results observed by Kapil, (2014) [13] & Saikia *et al*. (2016) [23]. Non-significant alteration in systolic arterial pressure in all the groups was noticed from base value. Propofol lowers blood pressure (SBP, DBP, and MAP) temporarily, owing to reduced peripheral vascular resistance, lower sympathetic outflow, and myocardial depression (Cullen & Reynoldson, 1993) [9]. Propofol infusion resulted in a reduction in systemic arterial blood pressure due to its direct negative inotropic action and direct drop in arterial and venous vascular tone (Jena *et al*., 2014) [12].

In ketofol group systolic arterial pressure remained stable during the anaesthetic duration, which could be attributed to a better and favourable synergistic impact of propofol and ketamine when used simultaneously (Schuszler *et al*., 2010) [27].

For both the groups diastolic arterial pressure at different time interval were noted and it was revealed that the difference was no significant. Whereas, intergroup comparison showed significant difference at 30 and 60 minute time interval between the two groups. In ketofol group DAP remains more stable and steady with in physiological range. The findings were similar to the results as reported by Henao-Guerrero *et al*. (2014) [11] & Paul *et al*. (2019) [21]. Propofol as sole induction agent downregulated diastolic arterial pressure and same has also been verified by Taboada & Leece (2014) [18] & Saikia *et al*. (2019) [21].

Mean arterial pressure did not differ significantly between the groups. Intergroup comparison reported significant variation at 75 min and 90 min time points. The findings of the current study were in agreement with the Kapil (2014) [13] who reported that the ketofol group have shown more stable hemodynamic compared with propofol. Mean arterial pressure retained when low dose of ketamine is combined with propofol and it also decreased the recovery time and also reduced the adverse effects of sole agent (Akin *et al*., 2005) [2]. Ketofol, on the other hand, increased systolic arterial pressure in humans compared to ketamine and propofol alone, according to Goh *et al*. (2005) [10]. Induction with ketofol had a higher MAP than propofol as investigated by (Martinez-Taboada *et al*., 2014) [18].

Non-significant alterations was noted within and between both the groups for Spo2. Both groups maintained levels of Spo2 within in the both groups, SpO2 was normal physiological range. Kapil, (2014) [13] reported that after induction of anaesthesia, no significant drop in Spo2 was seen in any of the three groups, and it stayed between 93 and 100 percent throughout the study period. During the anaesthetic phase, oxygen was continually supplied together with isoflurane, which helped to prevent intra-operative hypoxic situations. Sankar *et al*., (2011) [24] reported a reduction in Spo2 in dogs receiving continuous propofol infusions. The first drop in Spo2 could be related to a drop in respiratory rate as a result of respiratory depression caused by propofol anaesthetic dosages. Lee *et al*., (2017) [16] evaluated that during the general anaesthesia, Spo2 levels all groups' normal range, with no significant differences between them.

In propofol group fluctuating activity of Etco2 was observed whereas no significant difference observed within and between the groups. The results from present study were similar with the previous study done by Lee *et al*. (2017) [16].

Paul *et al*. (2019) [21] also reported evaluated that at different time interval, there was no significant variation in Etco2 value within the group and between the groups.

Conclusions

Significant difference was observed in respiration rate in ketofol group than to propofol group. Heart rate was comparatively maintained on higher side in the ketofol group than propofol group. Hemodynamic stability was more in the ketofol group than propofol group. Systolic, diastolic and mean arterial pressure maintained comparatively on higher side in the ketolfol group than propofol group.

Table 2: Mean ± SE values of propofol vs ketofol for different parameters at different time interval in elective ovariohysterectomy.

Parameters	Groups	Time interval (min)								
		Before Pre-anaesthetic	After Pre-anaesthetic	0	15	30	45	60	75	90
Heart rate (beats/min)	Group 1	121.50±5.37	125.83±4.63	117.17±6.76^{A}	110.67±8.35^{A}	111.00±4.90	109.00±5.12	110.83±6.20	108.33±6.26	117.50±11.83
	Group 2	119.30±5.02	131.23±6.24	138.83±5.06^{B}	131.33±5.19^{B}	126.00±4.16	123.8±4.09	123.00±5.29	121.20±5.03	126.20±5.21
Respiration rate (breaths/min)	Group 1	31.50±4.02^{a}	24.67±2.60^{ab}	12.3±1.20^{bA}	14.67±4.10^{b}	12.80±3.08^{b}	10.93±1.07^{b}	11.33±1.45^{bA}	10.33±0.98^{bA}	11.50±1.28^{bA}
	Group 2	33.00±1.91^{a}	29.00±5.41^{ab}	20.17±3.15^{bB}	22.67±2.99^{b}	17.83±3.06^{b}	16.83±2.62^{b}	17.83±2.33^{bB}	17.67±2.84^{bB}	19.67±2.44^{bB}
Rectal	Group	102.2±0.27^{a}	101.8±0.24^{ab}	100.5±0.24^{b}	99.62±0.20^{bc}	99.27±0.17^{bc}	99.22±0.50^{bc}	98.68±0.49^{c}	97.88±0.20^{c}	97.40±0.20^{c}

Temperature (^{0}F)	1									
	Group 2	102.3±0.17^a	101.6±0.18^b	101.1±0.12^{bc}	100.6±0.09^c	100.1±0.10^c	99.60±0.11^d	99.13±0.16^d	98.68±0.17^e	98.25±0.18^e

Value marked with superscript a,b,c,d,e differ significantly within rows at 5% level of significance.
Value marked with superscript A,B differ significantly within column at 5% level of significance.
Group 1- Propofol Group 2- Ketofol

Table 3: Mean ± SE values of propofol vs ketofol for different parameters at different time interval in elective ovariohysterectomy

Parameters	Groups	Time interval (min)						
		0	15	30	45	60	75	90
SAP (mm Hg)	Group 1	106.83±6.08	101.83±4.44	108.33±4.04	114.50±6.52	98.50±5.73	105.83±7.28	108.50±7.95
	Group 2	105.50±3.89	111.80±4.71	114.33±6.14	116.50±5.94	115.17±5.94	121.00±6.52	123.00±4.78
DAP (mm Hg)	Group 1	57.13±1.94	50.50±5.07	47.50±3.48^A	52.00±6.07	46.33±4.66^A	48.67±6.07	54.50±5.28
	Group 2	56.00±2.07	61.17±8.41	69.17±11.53^B	66.00±10.07	63.67±7.65^B	59.50±4.38	65.83±5.08
MAP (mm Hg)	Group 1	70.17±4.68	66.50±3.80	74.83±3.32	71.17±4.43	73.00±4.59	61.33±5.85^A	68.50±2.18^A
	Group 2	71.83±3.85	73.10±3.31	82.50±6.34	84.50±6.07	81.17±5.03	83.53±3.60^A	89.50±3.17^B

Value marked with superscript a,b,c,d,e differ significantly within rows at 5% level of significance.
Value marked with superscript A,B differ significantly within column at 5% level of significance.
Group 1- Propofol Group 2- Ketofol

Table 4: Mean ± SE values of propofol vs ketofol for different parameters at different time interval in elective ovariohysterectomy

Parameters	Groups	Time interval (min)						
		0	15	30	45	60	75	90
Isoflurane concentration (%)	Group 1	2.58±0.14	2.83±0.23	3.33±0.25	2.83±0.19	2.25±0.20	2.00±0.17	1.67±0.10
	Group 2	1.58±0.22	1.83±0.23	1.83±0.23	2.08±0.14	2.25±0.10	1.67±0.10	1.00±0.12
Spo2 (%)	Group 1	99.00±0.36	98.50±0.22	97.83±0.60	99.00±0.36	99.33±0.42	99.00±0.25	99.50±0.22
	Group 2	98.83±0.47	97.50±1.05	98.17±0.60	99.00±0.51	98.50±0.56	99.00±0.36	99.33±0.33
Etco2 (mm Hg)	Group 1	38.33±2.81	40.33±2.83	41.83±3.17	41.67±3.32	44.17±5.54	43.67±4.72	39.83±3.55
	Group 2	38.67±2.59	38.67±2.10	37.83±1.92	38.33±1.08	38.83±2.77	38.17±2.75	38.83±2.12

No significant difference within rows at 5% level of significance.
No significant difference within column at 5% level of significance.
Group 1- Propofol Group 2- Ketofol

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