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Evaluation of zoletil, ketamine midazolam and propofol CRI anaesthesia for ovariohysterectomy in dexmedetomidine premedicated female dogs with pyometra

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Abstract
The study was conducted on eighteen pyometra affected female dogs randomly divided into three group's i.e. groups A, B and C with six animals in each group to compare the physiological, biochemical and haemodynamic effects of CRI of zoletil, ketamine-midazolam and propofol balanced anaesthesia for ovariohysterectomy in female dogs with pyometra in the Teaching Veterinary Clinical Complex & Referral Veterinary Polyclinic, Indian Veterinary Research Institute (IVRI), Izatnagar, Uttar Pradesh, India. Animals of the three groups were administered with atropine at 0.04 mg/kg BW intramuscular followed by dexmeditomidine 15 µg/kg BW intramuscularly to animals of all the groups. Anaesthesia in the animals of group A was induced with zoletil (till effect), group B with ketamine-midazolam (till Effect), and group C with 1% propofol (till effect) then after 5 min it was maintained with CRI using a syringe infusion pump. In the present study all the three drugs are suitable to use as CRI drugs and can be safely used in dogs with pyometra undergoing ovariohysterectomy. However, propofol is better in maintaining physiological, haemodynamic and have shorter recovery period.

Keywords: Pyometra, dexmeditomidine, zoletil, ketamine-midazolam, propofol, constant rate infusion (CRI)

Introduction
CRI refers to administering a specified dose of drugs continuously in IV fluids (Taylor, 2014 and Lukasik, 2015) [4, 14] until the duration of treatment or surgery. In CRI, drugs are maintained in effective plasma, serum or tissue concentrations and avoid the pain peaks and valley related to repeated bolus administration (Taylor, 2014) [4]. Drugs to be administered are calculated according to CRI doses and administered with or without dilution in pre-determined rate or depending on patient needs, and it is titrated to different rates. When the infusion is started it takes a 3-5 drug half-life to achieve the desired plasma concentration, but it is too long. Alternatively a bolus induction drug dose is administered before CRI and the infusion starts according to the calculated dose (Hill, 2004 and Lukasik, 2015) [8, 14].
Dexmedetomidine is the active, d-isomer of medetomidine and it is an alpha 2 (α2) agonist (Millan *et al.*, 1996) [17]. Zoletil is an equal parts mixture of tiletamine and zolazepam. Zoletil gives moderate superficial, visceral and immediate analgesia and causes fast catalepsy followed by relaxation of muscles. Ketamine and tiletamine are commonly used as dissociative drugs in veterinary practice. The mechanism of action (MOA) is by antagonizing the n-methyl-daspartate (NMDA) receptors. So that neurotransmission is inhibited and various pharmacological effects achieved (Kavalali and Monteggia, 2012) [11]. Diazepam, midazolam and zolazepam are most commonly used benzodiazepines in veterinary practice. These are agonist of an inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Zakko *et al.*, 1999) [23], which bind to benzodiazepine receptors in the central nervous system and these receptors enhance the effects of GABA, this amplifies the function of chloride ion channel gating (Campo *et al.*, 2006) [3]. Propofol (2, 6-di-isopropylphenol). It is a short-acting IV anaesthetic drug (Bhat *et al.*, 2015) [2]. The MOA involves inhibition of the neurotransmitter GABA via GABA receptors.
Pyometra is a uterine infection in the female reproductive tract also called pyometritis and chronic purulent endometritis (Batista *et al.*, 2016) [1]. Ovariohysterectomy is the most effective and safest treatment (Nelson and Feldman, 1986) [19].

Materials and Methods

The dogs were randomly divided into three equal groups namely A, B, and C. Each group comprised of six animals (n=6). After surgical preparation, animals of the three groups were administered with atropine sulphate at 0.04 mg/kg BW IM then after 15 min dexmeditomidine was administered at 15 µg/ kg BW IM, animals of all the groups were left undisturbed for a maximum of 20 min on the ground to record the weak time and down time before induction. Anaesthetic drugs were administered via syringe infusion pump (SPA 112®, Alliance Medicaid, India). Immediately after inducing anaesthesia (till effect) using test drugs, the animal was intubated and maintained with CRI till the closure of the skin incision. Anaesthesia in the animals of group A was induced with zoletil (till effect) and then after 5 minutes it was maintained with zoletil (33 µg/kg/min) CRI using a syringe infusion pump. Anaesthesia in the animals of group B was induced with Ketamine-Midazolam at 1:2 ratio (till effect) and then after 5 min it was maintained with Ketamine (170 µg/kg /min) – Midazolam (6.7 µg/kg/min) at 1:2 ratio using a syringe infusion pump. Anaesthesia in the animals of group C was induced with 1% propofol (till effect) then after 5 min it was maintained with 1% propofol (150 µg/kg/min) CRI using a syringe infusion pump. The endotracheal tube was extubated once the tracheal reflex was regained.

Physiological and Haemodynamic observations

Both the parameters were recorded before the administration of drug at 0 min (base value) and 15 min after atropine, 10 min after dexmedetomidine (premedication), immediately after induction and then 10, 20, 30, 45, 60, 75, 90, 105 and 120 min after induction of anaesthesia in all the groups (Sharma *et al*., 2017) [21].

Physiological observations

Heart rate

Heart rate (beats/min) was recorded by veterinary multi-parameter monitor (Grubb *et al*., 2020) [6].

Respiratory rate

Respiratory rate (breaths/min) was assessed by chest wall excursions (Kaczka and Smallwood, 2012) [9].

Rectal temperature

Rectal temperature (°C) was measured by digital thermometer (Cugmas *et al*., 2020) [5].

Haemodynamic observations

Systolic Arterial Pressure (SAP) in mm Hg
Diastolic Arterial Pressure (DAP) in mm Hg
Mean Arterial Pressure (MAP) in mm Hg (Stamler, 1991) [22].

Biochemical observations

The blood samples collected in heparin vacutainer were centrifuged for 15 min at 3000 rpm following which the plasma was separated and collected in Eppendrof® tubes and stored at -20 °C till analysis. The plasma samples were subjected to the estimation of following parameters (Kalaiselvan *et al*., 2020) [10].

Plasma creatinine: Plasma creatinine was estimated by modified Jaffe's kinetic method using CREATININE KIT (Coral Clinical Systems, Uttarakhand) and expressed in µmol/L (Lumsden *et al*., 1979) [15].

Plasma urea nitrogen (PUN)

The PUN was estimated by the Modified Berthelot method using UREA KIT (Coral Clinical Systems, Uttarakhand) and expressed in mmol/L (Lumsden *et al*., 1979) [15].

Blood glucose

Blood glucose was estimated by GLUCOMETER (Morepen Laboratories LTD, India) using the fresh blood and expressed in mmol/L (Lumsden *et al.*, 1979) [15].

Plasma Insulin

Plasma insulin was quantified by INSULIN ELISA KIT (LABOR DIAGNOSTIKA NORD GmbH & Co.KG, Nordhem, Germany) and expressed in Pmol/L (Lumsden *et al.*, 1979) [15].

Results and Discussion

Physiological observations

Heart rate (HR)

In present study base values of HR of female dogs with pyometra were above the normal range (80-120 beats/minute) in all the groups. Similar findings were reported by Kempisty *et al*. (2013) [12] who reported that pyometra in dogs with septicemia or bacteremia and shock may ensue in tachycardia.

Respiratory rate (RR)

In the present study base values of respiratory rate were above the normal range (10-20 breaths/minute) in all the groups. It might be because of infection and toxemia (Kempisty *et al*., 2013) [12]. After administration of atropine, RR increased non-significantly (p>0.05) in all the groups as compared to the respective base values. This could be due to positive stimulation of cardiopulmonary system by primitive administration of atropine before pre-anaesthetic.

Rectal temperature (RT)

In the present study base values were slightly higher than the normal body temperature (38.3 to 39.2°C) in female dogs with pyometra. This could be due to uterine inflammation and secondary bacterial infection, as well as septicemia or bacteremia (Nelson and Feldman, 1986) [19].

Haemodynamic studies

In the present study base values of BP {systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP)} were within the normal range (SBP ranged from 110-160 mm Hg, DBP 80-100 mm Hg and MAP 85-120 mm Hg) in all the groups and BP increased non-significantly (p>0.05) in all the groups after atropine and dexmedetomidine administration as compared to the respective base values. It is reported that cardiac output (CO) may increase with atropine secondary to the increase in HR. Similar findings were recorded in the present study after atropine administration.

In group A, DBP decreased after significant (p<0.05) initial rise and SBP & MAP decreased after non-significant (p>0.05) initial rise after zoletil administration within the group. It is reported that decrease in BP could be due to tiletamine induced decrease in perfusion pressure and peripheral vascular resistance (Kwon *et al*., 2003) [13]. The findings reported in group B, were in agreement observations of with the Santhosh *et al*., (2013) [20] who reported that dogs anaesthetized with midazolam-dexmedetomidine, ketamine, initially showed increased SBP, DBP and MAP values which

decreased with the passage of time but the values remained within the normal physiological range. Higher values in group B might be due to the effect of pyometra and endotoxemia in the animals included in the study (Hagman *et al*., 2006) [7]. BP started to decrease in group C after induction of anaesthesia with propofol. It could be due a transient decrease caused by propofol in BP mainly due to a decrease in peripheral vascular resistance, decreased sympathetic outflow and myocardial depression (Bhat *et al*., 2015) [2].

Biochemical observations

Plasma creatinine and Plasma urea nitrogen

In the present study, base values of plasma creatinine and PUN did not differ significantly (p>0.05) among the groups and values were above the normal range (normal range of plasma creatinine is 50-170 µmol/L and PUN is 2.85-9.9 mmol/L) (Kaneko *et al*., 2008) [11]. Increased creatinine production from muscle damage and amino acid degradation could account for the observed increase in plasma creatinine values (Maddens *et al*., 2010) [16] and increased values of BUN indicates that the efficiency of kidneys to remove nitrogenous wastes from the circulation is affected.

Blood glucose

Hyperglycemia is a common feature of patients with sepsis. However, the base values of blood glucose were within the normal limits (4.4-6.7 mmol/L) (Kaneko *et al*., 2008) [11] in the present study in all the groups.

Insulin

The base values of plasma insulin were within the normal limits (36-144 pmol/L) (Kaneko *et al*., 2008) [11] in all the groups but decreased significantly (p<0.05) from the baseline towards the end of the observation period after administration of various pre-anaesthetics and anaesthetics in all the groups. Results of the present study were in accordance to earlier studies by Sharma *et al*. (2017) [21] who reported that insulin secretion is decreased due to dexmedetomidine (α2 agonist) that activates α2 receptors on pancreatic β cells, which lead to inhibition of insulin release.

Table 1: Mean ± SE values of physiological parameters at different time intervals in various groups of female dogs with pyometra

Parameters	Group	Baseline	Premedication	Before induction	Maintenance								
					10 min	20 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
HR (beats per min)	A	128.5 ±7.1^{ab}	135.5 ±8.5^{a}	103.4 ±4.2^{b}	151 ±12.4^{a}	148.8 ±10.8^{a}	137.2 ±9.3^{a}	145.8 ±10.4^{a}	139.2 ±9.2^{aA}	120.2 ±6.8^{abAB}	134 ±9.3^{aA}	127.5 ±7^{ab}	120 ±6.8^{ab}
	B	134.3 ±8.92^{ab}	140.6 ±10.3^{a}	105.21 ±4.32^{b}	147.2 ±10.9^{a}	135 ±9.1^{b}	140.8 ±9.8^{a}	134.8 ±8.9^{a}	125.8 ±6.2^{abAB}	138.2 ±9.9^{aA}	119.4 ±5.8^{abAB}	124.3 ±6.1^{ab}	117.2 ±5.4^{ab}
	C	131.8 ±8.7^{ab}	138.5 ±9.2^{ab}	109.35 ±4.97^{b}	107 ±4.54^{bA}	105.8 ±4.39^{bA}	100 ±4.8^{bA}	97 ±3.2^{bB}	92.5 ±3.3^{bB}	95 ±3.7^{bB}	98.2 ±3.5^{bB}	105.5 ±4.1^{b}	100.7 ±4.3^{b}
RR (breaths per min)	A	29±2.43^{a}	32.5 ±2.63^{a}	22.8 ±1.11^{ab}	14.5 ±0.48^{b}	16.3 ±0.69^{b}	24.2 ±1.48^{ab}	27.5 ±1.91^{aA}	25.5 ±1.68^{ab}	25.5 ±1.66^{ab}	27 ±1.78^{a}	28.5 ±2.31^{a}	28.3 ±2.32^{a}
	B	28±2.35^{a}	34.7 ±2.63^{a}	23.7 ±1.29^{ab}	12.2 ±0.41^{b}	13.5 ±0.39^{b}	20.8 ±0.98^{ab}	16.5 ±0.68^{b}	17 ±0.71^{b}	18.8 ±0.88^{b}	21.17 ±1.2^{ab}	26 ±1.37^{ab}	25.2 ±1.6^{ab}
	C	29±2.47^{a}	32.2 ±2.62^{a}	21.8 ±2.63^{a}	14.8 ±0.43^{b}	12 ±0.34^{b}	12 ±0.35^{b}	12.3 ±0.37^{b}	19.5 ±0.91^{ab}	19.8 ±0.92^{ab}	25.7 ±1.7^{ab}	24.17 ±1.5^{ab}	24.2 ±1.4^{ab}
RT (^{o}C)	A	39.47 ±0.58^{a}	38.83 ±0.56^{a}	38.19 ±0.55^{a}	38.63 ±0.43^{a}	38.19 ±0.45^{a}	37.97 ±0.33^{ab}	37.37 ±0.36^{ab}	35.63 ±0.12^{b}	36.6 ±0.2^{b}	36.43 ±0.22^{b}	36.67 ±0.24^{b}	36.03 ±0.23^{b}
	B	39.52 ±0.52^{a}	38.81 ±0.41^{a}	38.62 ±0.42^{a}	38.34 ±0.41^{a}	37.8 ±0.42^{ab}	37.6 ±0.39^{ab}	35.02 ±0.11^{b}	35.42 ±0.14^{b}	37.5 ±0.34^{ab}	35.13 ±0.13^{b}	36.91 ±0.22^{b}	36.98 ±0.23^{b}
	C	39.43 ±0.56^{a}	38.85 ±0.52^{a}	38.64 ±0.51^{a}	38.71 ±0.41^{a}	37.9 ±0.43^{ab}	37.7 ±0.45^{ab}	35.05 ±0.15^{b}	37.54 ±0.39^{ab}	35.43 ±0.11^{b}	36.31 ±0.23^{b}	36.68 ±0.16^{b}	36.15 ±0.21^{b}

Small letters indicate significance (p<0.05) in a row Capital letters indicate significance (p<0.05) in a column * Groups or time with the common letters do not differ significantly

Table 2: Mean ± SE values of haemodynamic parameters at different time intervals in various groups of female dogs with pyometra

Parameters	Group	Baseline	Premedication	Before induction	Maintenance								
					10 min	20 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
SBP (mm Hg)	A	154.17 ±9.32^{ab}	158 ±9.27^{ab}	168 ±10.84^{a}	164.2 ±10.67^{a}	169.17 ±10.36^{a}	173.83 ±10.36^{a}	165.83 ±10.4^{a}	159.5 ±9.5^{a}	155 ±9.92^{ab}	140.83 ±7.19^{b}	145.5 ±7.72^{ab}	141.33 ±7.35^{ab}
	B	152.83 ±9.77^{ab}	157.33 ±9.66^{ab}	159.67 ±10.19^{a}	160.83 ±10.98^{a}	161.17 ±10.31^{a}	161.17 ±10.84^{a}	152 ±9.89^{ab}	155 ±9.92^{ab}	158.67 ±9.74^{a}	158.67 ±9.56^{a}	143.5 ±7.17^{ab}	139.67 ±6.7^{b}
	C	153.5 ±9.57^{ab}	158.5 ±9.38^{ab}	160.5 ±10.08^{a}	124.5 ±4.44^{bA}	129.83 ±5.32^{bA}	130.67 ±5.61b^{A}	154.5 ±9.44^{ab}	153.6 ±9.42^{ab}	152.5 ±8.52^{ab}	143.67 ±6.4^{ab}	144.67 ±7.35^{ab}	140.67 ±6.4^{b}
DBP (mm Hg)	A	83 ±3.47^{b}	84 ±5.18^{b}	116.33 ±6.8^{ab}	130.3 ±8.21^{a}	127.7 ±7.98^{a}	125.7 ±7.52^{a}	128 ±7.28^{a}	124.3 ±7.71^{a}	121.67 ±7.86^{a}	108± 6.7^{ab}	93.67 ±5.63^{b}	85.83 ±4.6^{b}
	B	85.33 ±4.63^{b}	85.17 ±5.15^{b}	117.67 ±6.23^{ab}	122.7 ±6.75^{a}	122.4 ±6.1^{a}	125.5 ±7.74^{a}	127.2 ±7.53^{a}	122 ±7.63^{a}	122.67 ±6.92^{a}	103.33± 5.6^{ab}	96.33 ±4.10^{b}	84 ±4.69^{b}
	C	84.17 ±4.34^{b}	85.5 ±4.79^{b}	112.56 ±5.06^{ab}	87.7 ±4.99^{bA}	84.3 ±4.16^{bA}	92.7 ±5.26^{bA}	98.67 ±5.66^{bA}	98.1 ±5.71^{bA}	95.5 ±4.34^{bA}	87.83 ±4.73^{b}	91.33 ±4.39^{b}	83.17 ±3.21^{b}
MAP (mm Hg)	A	113.33 ±5.9^{ab}	114.83 ±5.04^{ab}	138.33 ±7.72^{a}	142 ±9.48^{a}	135.33 ±7.57^{a}	147.33 ±9.27^{a}	133.33 ±7.97^{a}	140.83 ±9.41^{a}	135 ±7.87^{a}	123.33 ±6.2^{ab}	116.5 ±5.77^{ab}	118.67 ±5.42^{ab}
	B	116.83 ±5.29^{ab}	118.7 ±5.7^{ab}	135 ±7.82^{a}	140.17 ±9.9^{a}	137 ±7.23^{a}	135.33 ±7.71^{a}	144.33 ±9.68^{a}	135.17 ±7.17^{a}	124.33 ±6.46^{ab}	125.5 ±6.6^{ab}	118.33 ±5.09^{ab}	114.17 ±5.05^{ab}
	C	118 ±5.67^{ab}	118.67 ±6.28^{ab}	132.5 ±7.24^{a}	90 ±3.27^{bA}	95.83 ±4.13^{bA}	98.83 ±4.71^{bA}	129.67 ±6.44^{ab}	128.33 ±6.65^{ab}	120.17 ±5.84^{ab}	112.33 ±5.6^{ab}	117.1 ±5.32^{ab}	113 ±5.13^{ab}

*Small letters indicate significance (p<0.05) in a row * Capital letters indicate significance (p<0.05) in a column * Groups or time with the common letters do not differ significantly

Table 3: Mean ± SE values of biochemical parameters at different time intervals in various groups of female dogs with pyometra

Parameters	Group	Time (min)			
		0	30	60	120
Plasma Creatinine (µmol/L)	A	260.55±5.67	260.02±5.61	258.51±4.15	257.11±5.19
	B	262.36±5.9	261.22±5.25	261.84±3.97	259.11±4.26
	C	262.3±5.73	260.76±5.01	255.92±4.5	255.1±5.7
Plasma Urea Nitrogen (mmol/L)	A	23.34±0.17	24.66±0.24^{a}	23.75±0.16	22.64±0.12
	B	23.62±0.19	24.98±0.26^{a}	23.53±0.16	22.92±0.11
	C	23.27±0.16	24.47±0.22^{a}	22.63±0.12	22.5±0.12
Blood glucose (mmol/L)	A	5.16±0.14^{a}	6.47±0.17^{b}	7.13±0.23^{bc}	8.39±0.24^{bc}
	B	5.16±0.14^{a}	6.82±0.18^{b}	8.14±0.28^{bc}	9.26±0.25^{c}
	C	5.16±0.14^{a}	7.29±0.18^{bc}	8.17±0.24^{bc}	9.11±0.27^{c}
Plasma insulin (pmol/L)	A	49.02±0.76^{a}	40.99±0.66	41.83±0.61	37.17±0.53
	B	49.04±0.78^{a}	42.6±0.68	36.34±0.62	35.5±0.64
	C	48.48±0.77^{a}	41.37±0.68	39.2±0.64	33.94±0.52

* Small letters indicates significance (p<0.05) in a row

Conclusions

- Propofol anaesthesia leads to better and faster recovery as compared to zoletil and ketamine-midazolam CRI.
- Propofol resulted in better physiological and haemodynamic stability than compared to zoletil and ketamine-midazolam CRI for ovariohysterectomy in bitches with pyometra.

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