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Propofol and ketamine CRI in dexmedetomidine and butorphanol premedicated dogs

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Abstract
The study was carried out to evaluate propofol and ketamine CRI in dexmedetomidine and butorphanol pre-medicated dogs undergoing elective ovariohysterectomy. Animals were randomly divided into two Groups (A and B) comprising six animals in each. All the animals were administered glycopyrrolate @ 0.01 mg/kg IM. Fifteen minutes later dexmedetomidine 5µg/kg IV and butorphanol 0.1mg/kg IV and two minutes later induction and maintenance of anaesthesia was done with propofol in Group A and ketamine in Group B. The mean induction times (Sec) in Group A and B were recorded as 34.67 ± 2.12 and 36.67±1.63, respectively. The induction doses of propofol and ketamine were recorded as 0.68± 0.06 and 2.63±0.26 mg/kg, respectively. The recovery time were recorded as 10.25±0.44 and 14.83±1.26 min in Group A and B, respectively. The maintenance dose of propofol and ketamine for CRI were recorded as 0.24±0.01 and 0.013±0.60 mg/kg/min, respectively in Group A and B. Quality of anaesthesia was excellent in both the group and the clinical parameters remained with the physiological limit.

Keywords: propofol, ketamine, dexmedetomidine, butorphanol, CRI

Introduction
Inhalation anaesthetics are used widely for the anaesthetic management in canine patients. They are unique among the anaesthetic drugs because they are administered and in large part removed from the body via the lungs. Inhalation agents are preferred because their pharmacokinetic characteristics favour predictable and rapid adjustment of anaesthetic depth. However, a special apparatus and constant monitoring is necessary to deliver the inhalation agents. Total intravenous anaesthesia (TIVA) either with repeated bolus injection or continuous rate infusion (CRI) has been emphasized in the recent years as it makes the anaesthetic management easier especially when the surgeon himself has to control the anaesthesia, which is frequently the situation in most of veterinary hospitals in the country. Anaesthetic protocols involving multiple agents from different classes to achieve ideal components of general anaesthesia and at the same time mitigating the side effects of an individual agent has been emphasized. Therefore, the present study has been undertaken with to compare the propofol, ketamine continuous rate infusion in butorphanol and dexmedetomidine pre-medicated dog for ovariohysterectomy.

Materials and Methods
Twelve numbers of female dogs presented for elective ovariohysterectomy were randomly divided into two groups (Group A and B) comprising of six animals in each group. The animals in all the groups were administered with glycopyrrolate @ 0.01 mg/kg IM. Fifteen minutes after administration of glycopyrrolate, the animals were administered dexmedetomidine @5µg/kg IV and Butorphanol @ 0.1mg/kg IV. Two minutes after administration of dexmedetomidine and butorphanol induction and maintenance of anaesthesia was done with propofol in Group A and with ketamine in Group B. The heart rate, respiratory rate and rectal temperature were recorded at 0 minute (before premedication) and 20 minutes, 40 minutes and 60 minutes (during maintenance). Induction Time was recorded (in seconds) from administration of the induction agent till the animal is anaesthetized. The mean dose (mg/Kg) required for induction and maintenance of anaesthesia were recorded in both the groups. The overall quality of induction was scored as per the method described by Amengual *et al.* (2013) [2] and scores were given as 0- Calm transition, no paddling, 1- Occasional, slow paddling movements, 2- Moderate, sustained paddling movements and 3- Marked paddling, struggling or vocalisation. Intubation quality was assessed as per the method described by Amengual *et al.* (2013) [2] and scores were given as 0- Easy intubation, 1- Mild coughing, 2-

Pronounced coughing and 3- Swallowing, coughing and gagging. The quality of analgesia was assessed as per the method described by Sabbe *et al*. (1994) [23] and scores were given as 0- Normal pedal reflex, 1- Immediate withdrawal, 2- Slow reflex, 3- Withdrawal of foot only after pinching with increased intensity for 3 seconds and 4-No response. The muscle relaxation was judged as per the method described by Ahmad *et al*. (2013) [1] and scores were given as 0- Not allowing opening of the jaws, 1- Resistant to opening of the jaws and closed quickly, 2- Less resistance to opening of the jaws and closed slowly and 3- No resistance and jaws remain open. The anaesthetic depth was assessed as per the method described by Ahmad *et al*. (2013) [1] and scores were given as 0- Intact and strong (quick blink), 1- Intact but weak (slow response), 2- Very weak (very slow and occasional response) and 3- Abolished (no response). Recovery time (minutes) was recorded as time from discontinuation Vaporizer setting till return of swallowing reflex and removal of endotracheal tube. Quality of recovery was assessed as per the method described by Jimenez *et al*. (2012) [12] and scores were given from 1to 6. The data obtained were analyzed using statistical package SPSS version 16.

Results and Discussion

The heart rate at different time intervals decreased significantly ($P< 0.05$) in Group 20 min (101.67±5.31) continued to decrease at a slower rate in the subsequent period. In Group B, the heart rate increased significantly ($P< 0.05$) initially at 20 min (133.83±3.48) and continued to increase till the end of the observation period. The decrease in heart rate observed in Group A might be due to the effect of butorphanol and dexmedetomidine as both the drugs caused decrease heart rate in animals as mentioned by Greene *et al.* (1990) [8]. The dexmedetomidine causes a vasoconstriction in both the pulmonary and systemic circulations initially and then elicits a decrease in heart rate and cardiac output with a slight depressive effect on ventilation (Pascoe, 2015) [22]. In Group B, the rise in heart rate might be due to cardiac stimulatory effects of ketamine Kumar *et al.* (2014) [14]. Ketamine stimulates the cardiovascular system resulting in increased heart rate principally through the sympathetic nervous system (Kolawole, 2001) [13]. Ketamine has an antagonistic interaction with mono-aminergic, muscarinic and nicotinic receptors and produces anticholinergic symptoms (Pai and Heining, 2007) [21]. The respiratory rate decreased significantly ($P< 0.01$) in both the groups from pre-induction values. The decreased respiratory rate observed might be due to depression of respiratory centre caused by ketamine (Narayanan *et al.* 2011) [19] and propofol (Suarez *et al.* 2012) [28]. The respiratory depression with ketamine anaesthesia might also be due to airway relaxation by acting on various receptors, inflammatory cascades and bronchial smooth muscles as reported by Goel and Agrawal (2013) [7]. The rectal temperature decreased at different time intervals in both the groups after administration of anaesthesia till the end of the observation period which was significant ($P< 0.05$) in Group B. The decreased rectal temperature recorded in the present study might be due depression of the thermoregulatory centre or depression of the basal metabolic rate or reduction in peripheral circulation or due to muscle relaxation (Ahmad *et al.* 2013) [1].

The mean induction times (Sec) in Group A were recorded as 34.67±2.12 and in Group 36.67±1.63, respectively. The shorter induction times observed in the present study might be due to the synergistic effect of dexmedetomidine and butorphanol which caused sufficient degree of sedation prior to induction. Dexmedetomidine has rapid onset of action owing to its lipophilic properties (Arunkumar *et al.* 2017) [3]. Congdon *et al*. (2011) [5] also observed potent sedation enabling minor clinical procedures in dogs with intramuscular administration of dexmedetomidine @10 mcg/kg. Similarly, Trimble *et al*. (2018) [32] also reported high sedation with butorphanol and dexmedetomidine in dog. The induction dose (mg/kg) of propofol in Group A was 0.68± 0.06 and ketamine in Group B was 2.63±0.26. The induction doses of propofol and ketamine recorded in the present study were lower than their general recommended doses with and without premedication in dog. The reduction in the total dose of induction agent in the present study might be due to the synergistic action of dexmedetomidine and butorphanol (Jena *et al*. 2014) [11] with the induction agents. The premedication with alpha2adrenoceptor and opioid might have reduced the induction dose of propofol and ketamine. A reduction in the induction dose of propofol by 20 to 80% when administered in combination with sedative or analgesic agents was reported by Short and Bufalari (1999) [26]. Sharma *et al.* (2014) [25] also observed similar reduction in dose of ketamine with butorphanol and dexmedetomidine premedication in dogs and opined that dexmedetomidine along with butorphanol reduced the induction dose rate of ketamine up to 61%. All the groups were recorded with induction score of zero. During the anaesthetic induction the animals in all the groups were recorded with calm transition, without paddling movement, salivation, nausea and vomiting. An excellent jaw relaxation was observed in animals of both the groups and all the animals were recorded with easy intubation. The analgesic score were recorded as 4 in both the groups. The animals showed excellent analgesia sufficient for performing surgical operation showing no response to noxious stimuli and tolerated the surgery well. The analgesia observed in the present study might be due to the synergistic effect of butorphanol and dexmedetomidine (Kuusela *et al.* 2000) [15] as propofol provides minimal analgesia (Neto *et al.*2007) [20] although ketamine provides profound analgesia (Hall *et al*. 2014) [9]. Butorphanol has strong agonist activity at the kappa and sigma receptors. It exerts its effect by inhibiting the transmission of nociceptive stimulation in the dorsal horn of the spinal cord, activating descending inhibitory pathways, inhibiting supra spinal afferent pathways and causing a decrease in the release of neurotransmitters in the spinal cord (Schnellbacher, 2010) [24]. The analgesic effect by dexmedetomidine is mediated at spinal level and by interruption of nociceptive pathways to the ventral root of the dorsal horn which reduce spinal reflexes (Talukder and Hikasa 2009) [30]. Dexmedetomidine activates α2-adrenargic receptors reducing the transmission of nociceptive signals like substance P (Bekker and Sturaitis, 2005) [4]. Ketamine inhibits ion-channels at the membrane levels and acts on the opioid receptors to exhibit antinociceptive effects (Sleigh *et al.* 2014 [27], Demirkan *et al.* 2002 [6]). The muscle relaxation score were recorded as three in both the groups. All the animals showed excellent muscle relaxation enabling intubation and the surgical procedure. The excellent muscle relaxation observed in all the groups might be due to dexmedetomidine, as all alpha-2 adrenoceptor agonists including dexmedetomidine are known to produce good muscle relaxation (Lemke, 2007) [16] which is attributed to inhibition of intraneuronal transmission of impulses by alpha-2 agonists

at the level of central nervous system (Marjorie 2001) [17]. The muscle relaxation might also be enhanced due to butorphanol, propofol and isoflurane as co-administration of anaesthetics, sedatives, hypnotics or opioids with dexmedetomidine is likely to lead to an enhancement of their effects (Naaz and Ozair, 2014) [18]. The animals in both the groups had an abolished palpebral reflex during the procedure and scored as 3. The depth of anaesthesia observed in the present study might be attributed to the synergistic effects of dexmedetomidine and butorphanol with the induction and maintenance agents (Naaz and Ozair, 2014) [18] and it might also be attributed to the action of propofol and ketamine (Hazra *et al.* (2008) [10].The recovery time (min) were recorded as 10.25±0.44 and 14.83±1.26 in Group A and B, respectively. The shorter recovery time recorded might be due to the shorter duration of sedative action of dexmedetomidine due rapid biotransformation with elimination half-life of 47 min (Kuusela *et al.* 2000) [15]. It might be attributed to rapid redistribution from the brain to other tissues, quick biodegradation of the agents by the hepatic enzyme systems and efficient elimination from plasma by metabolism as described by Watkins *et al*. (1987) [33] and Zoran *et al.* (1993) [34]. In Groups A, 33.33% animals were recorded with score 3 and 66.66% were recorded with score 4. In Group B 33.33% animals scored 3, 50.00% animals scored 4 and 16.66 % animals scored 5. The smooth recovery observed in the present study might be due to the combined effect of pre-anaesthetic and anaesthetic agents. The mean values of maintenance dose of (mg/kg/min) propofol and ketamine were recorded as 0.24±0.01 and 0.013±0.60 respectively, in Group A and B. The reduction in the maintenance dose in the present study might be due to the use of dexmedetomidine and butorphanol as pre-anaesthetic agents. Reduction in maintenance dose of anaesthetic agent due to use of sedatives and opioids were also reported by various workers. Intravenous injection of butorphanol at dose rate of 0.1 and 0.3 mg/kg reduced the anaesthetic requirement by 11% and 16%, respectively (Trim, 1983) [31].

Conclusion

Dexmedetomidine and butorphanol premedication reduced the doses of propofol and ketamine for induction and maintenance of anaesthesia. The total intravenouos anaesthesia with propofol CRI was found to be better than with ketamine.

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