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Effect of dexmedetomidine/midazolam - ketamine anaesthesia on physiological and haematological parameters in dogs undergoing elective ovariohysterectomy

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Abstract
The present study was conducted on 28 female dogs irrespective of age, breed and body weight brought for elective ovariohysterectomy which were randomly divided into two groups comprising of 14 animals in each group. Sedation was achieved by administration of Dexmedetomidine and Midazolam in group-I and II, respectively. Heart rate was decreased significantly in group-I, while increased significantly in group-II after sedation. Respiratory rate and rectal temperature showed significant decline after sedation in both the groups. Haemoglobin and TEC values were decreased significantly after pre medication and afterwards and there was non-significant decrease at the end of surgery in group-II as compared to group-I. In both the groups, there was non-significant decrease in TLC and PCV values at different time intervals. From the present study, it was concluded that Midazolam/Dexmedetomidine anaesthetized with ketamine provide adequate sedation in the dogs undergoing elective ovariohysterectomy surgery. Midazolam/ Dexmedetomidine provides better haemodynamic and respiratory stability when used as a pre-anaesthetic for induction with ketamine in the dogs undergoing elective ovariohysterectomy surgery.

Keywords: Dexmedetomidine, dogs, haematological, midazolam, physiological, ovariohysterectomy

Introduction
Anaesthesia is essential for successful surgical intervention to achieve complete immobilization, muscle relaxation and unconsciousness. None of the anaesthetic agent is considered to be a perfect even after the development of many new anaesthetic agents. Therefore, to achieve a perfect anaesthesia a combinations of anticholinergics, sedatives, analgesics and general anaesthetics should be used to induce anaesthesia using lower doses of each drug than that would be required if each component were used alone (Tonner, 2005) [60]. Use of single drug for achieving anaesthesia should be discouraged due to toxicity and complications associated with high dose, a combination of medicines from various pharmacological properties is advocated to achieve balanced anaesthesia. In recent decades, the studies investigating cardiovascular changes are even more necessary as incidence of cardiac diseases increases with age and there is need to identify sedative protocols that cause minimal cardiovascular and haemodynamic changes. In veterinary practice, mortality due to cardiovascular and respiratory alterations during anaesthesia is of major concern in canines; although, gastrointestinal, neurological, renal and hepatic changes also have been reported (Redondo *et al.*, 2007) [48]. Thus, it is essential to understand the potential depressant effects of anesthetic drugs on the cardiovascular system to reduce mortality rate and perform anaesthetic procedures smoothly (Bille *et al.*, 2014) [6]. Cardiac affections are routinely diagnosed on the basis of history, clinical signs, physical examination, radiography and auscultation of heart and lung sounds (Kraetschmer *et al.*, 2008; Prieto *et al.*, 2009; Crosara *et al.*, 2010; Falk *et al.*, 2010) [29, 43, 13, 16].

Materials and Methods
The present study was conducted on 28 female dogs irrespective of age, breed and body weights brought to the Department of Veterinary Surgery and Radiology, College of Veterinary Sciences, LUVAS, Hisar for elective ovariohysterectomy. These animals were randomly divided into two groups comprising of fourteen animals in each group as mentioned below:

Groups	No. of animals	Premedication agents	Induction agent	Maintenance agent
I	14	Atropine (0.04 mg/kg b.wt IM) Meloxicam (0.3 mg/kg b.wt IM)) Dexmedetomidine (15 µg/kg b.wt IM)	Ketamine @ 5mg/kg b.wt I/M Till effect	Dexmedetomidine + Ketamine
II	14	Atropine (0.04 mg/kg b.wt IM) Meloxicam (0.3 mg/kg b.wt IM)) Midazolam (0.5 mg/kg b.wt IV	Ketamine @ 5mg/kg b.wt I/V Till effect	Midazolam + Ketamine

Physiological and haematological parameters were evaluated in all the animals of the present study.

1. Physiological Parameters

A thorough physical examination was performed on all the animals. Rectal temperature was measured with the help of a digital thermometer. Respiratory rate was noted by counting the chest movements. Ausculation was carried out starting from the base of heart to the apex from left side to record heart rate. Heart rate was noted from the point of maximal intensity. Physiological parameters were recorded pre-operatively, after 10 min. of Dexmedetomidine/ Midazolam administration, at induction with Ketamine, after 10, 20 and 30 min. of skin incision respectively and at the end of surgery.

2. Haematology

Two milliliters of blood was collected in sterile EDTA vials from cephalic vein pre-operatively, after 10 minutes of sedation and at the end of the surgery for the analysis of haematological parameters *viz*., Haemoglobin (Hb), Total erythrocyte count (TEC), Total leukocyte count (TLC), Packed cell volume (PCV), Total platelet count and Differential leukocyte count (DLC).

3. Statistical Analysis

The statistical analysis was conducted via SPSS software. Two-way ANOVA test was used to determine significant difference between different groups and between different time intervals. All the data values were expressed as Mean ± SE and pair wise comparison was done using Duncan Test. P-values <0.05 was considered as statistically significant.

Results and Discussion

Heart rate (beats/minute) in group I decreased significantly ($p< 0.05$) and in group II increased significantly ($p< 0.05$) at 10 minutes after pre-medication from respective base values. Decrease in heart rate recorded after dexmedetomidine has been attributed to activation of parasympathetic tone (Bloor *et al.,* 1992) [7]. Alvaides *et al.* (2008) [7] also recorded that administration of atropine sulphate caused increase in the heart rate which remained significantly higher for five minutes in spite of systemic administration of dexmedetomidine, however heart rate was progressively declined after treatment with dexmedetomidine. Murdock *et al.* (2020) [36] observed that heart rate was significantly elevated in alfaxalone-butorphanol-midazolam group than alfaxalone-butorphanol-dexmedetomidine group at 90 minutes after treatment. Yoo *et al.* (2002) [65] reported an increase in heart rate after pre-medication with atropine and midazolam. In both the groups, heart rate was increased significantly after induction from pre anaesthetic values. Zielmann *et al.* (1997) [66] reported that ketamine increases cardiac output and heart rate along with significant increase in blood pressure thus it is having stimulatory effect on heart. Increase in heart rate after ketamine administration may be due to its action on sympathetic trunk and inhibition of neuronal uptake of catecholamine by sympathetic nerve endings (Tweed *et al.,* 1972; Ivankovitch et al., 1974) [62, 21] or may be due to increase in central release of catecholamine resulting in tachycardia (Hardie and Lukasik, 2007) [18]. Kumari (2015) [31] stated that the mild decrease in heart rate from 60 or 90 minutes of the observation was due to the fact that duration of action of atropine sulphate is 60 to 90 minutes. (Muir, 2007) [34] Which compromised the depressant effect of dexmedetomidine or dexmedetomidine – midazolam in propofol induced anaesthesia. At T10 (after 10 min. of skin incision) the heart rate was decreased significantly in both the groups. Afterwards, there were non-significant changes at T20, T30 and at the end of the surgery. There was significant different between the groups after preanaesthetic, after induction, at T10, T20, T30 and at the end of surgery. The value of respiratory rate in both the groups decreased significantly ($p< 0.05$) at 10 minutes after pre-medication from respective base values. Rafee (2017) [46] observed a non-significant decline in respiratory rate with dexmedetomidine (I/M) alone or in combination with butorphanol. Similarly, Patond (2016) [41] observed that dexmedetomidine caused a significant decrease in respiratory rates irrespective of the dose which persisted during propofol anaesthesia in the surgery. Alpha 2 agonists, like dexmedetomidine has been known to produce respiratory depression caused by activation of the alpha 2 adrenergic pathways which lead to inhibition of locus coeruleus neurons (Oyamada *et al.,* 1998) [40]. Kojima *et al.* (2002) [27] also observed significant decrease in respiratory after induction with propofol in canine premedicated with midazolam-butorphanol combination. Butola and Singh (2007) [9] also observed significantly decrease in respiratory rate after pre-medication with midazolam in canine. Afterwards, there is non-significant changes at induction, T10, T20, T30 and at the end of surgery. There was no significant difference in between the groups at different time interval. Chang *et al.* (2009) [11] reported that midazolam caused more respiratory depression as compared to dexmedetomidine in the rabbit. The mean values of rectal temperature decreased significantly ($p< 0.05$) in both the groups at 10 minutes after pre-medication followed by non-significant decrease at induction and after 10 min. of skin incision. Afterwards, there was significant decrease at T20, T30 (after 20 min. and 30 min. of skin incision, respectively) and at the end of the surgery in both the groups. Seo *et al.* (2015) [51] observed that rectal temperature decreased non-significantly after administration with butorphanol-midazolam combination in canines as also recorded in group II of the present study. Kellihan *et al.* (2015) [24] observed a non-significant increase in rectal temperature at 20 minutes whereas a significant decrease at 40 minutes after administration of dexmedetomidine and butorphanol combination. Raekallio *et al.* (2005) [45] also observed a consistent decrease in rectal temperature after intravenous administration of dexmedetomidine. In support with present study, Butola and Singh (2007) [9] also recorded non significant decrease in rectal temperature by administration of midazolam alone in dogs. Effects of dexmedetomidine, midazolam and dexmedetomidine-midazolam premedication

in propofol induced anaesthesia in dogs during ovariohysterectomy contributing factor to a decreased body temperature in midazolam premedication (Ramaswamy *et al.*, 1991) [47]. Schroeder and Smith (2011) [50] reported the decrease in body temperature by administration of combination of midazolam and butorphanol. Virtanen (1989) [64] also reported that sedative or anaesthetic drug might induced a decrease in rectal temperature due to decreased muscular activity and also by direct action on the hypothalamus. However, in the present study the rectal temperature decreased but the values of rectal temperature were within physiological range.

In group I, there was non-significant decrease in Hb, PCV and TEC at different time intervals. In group II, the value of Hb decreased significantly after pre medication and afterwards there was non-significant decrease at the end of surgery. Between the groups, there were no significant differences in Hb at different time intervals. Between the groups there were no significant differences in TEC at base line and after pre medication. There was significant difference between the groups at the end of the surgey. Between the groups there was significant difference in PCV values after 10 minutes of pre medication and at the end of the surgery. Research of the present study conformed to the observation of Biermann *et al.* (2012) [5] who observed that PCV and Hb decreased after midazolam-butrophanol administration. Dinesh (2017) [15] also reported a non-significant reduction in haemoglobin and PCV during premedication with midazolam- pentazocine followed by induction with propofol and maintenance of anaesthesia with isoflurane. A similar finding was also reported by Kelawala *et al.* (1991) [23] in goats and by Gill *et al.* (1996) [17] in canines during anaesthesia. A similar decrease in haemoglobin with alpha-2 agonists was also reported by Amarpal *et al.* (1998) [3] and Ahmad (2010) [1] in canines and by Hugar (1993) [19] and Kumar and Thurmon (1979) [30] in goats. The similar results were also observed during epidural anaesthesia with medetomidine in caprine (Kinjavdekar *et al.*, 1999) [26]. Decreases in PCV were also reported in adult horses following single intravenous/intramuscular doses of xylazine/detomidine (Wagner and Hitchcliff, 1991). Decline in haemoglobin and PCV values might be due to pooling of circulating red blood cell in spleen or other reservoirs. Pooling occurred as a secondary effect of reduced sympathetic stimulation (Surbhi *et al.*, 2010 and Singh *et al.*, 2013) [58]. However, Costa *et al.* (2013) [12] suggested that the reduction in PCV and Hb might be due to sequestration of erythrocyte in non-splenic sites. They also reported that propofol did not cause measurable splenic enlargement but caused a decrease in Hb and PCV (Surbhi *et al.*, 2010 and Singh *et al.*, 2013) [58]. However, Costa *et al.* (2013) [12] reported sequestration of erythrocyte in non-splenic sites and correlation between PCV and spleen size was not observed with propofol anaesthesia. Tranquilli *et al.* (2007) [61] observed that anaesthetic-induced vasodilatation also contributes to the decrease of haemoglobin. Similarly, Naghibi *et al.* (2002) [37] reported passage of many red blood cells to microcirculation due to vasodilatation which might cause decrease in haemoglobin level in peripheral circulation. Decrease in Hb and PCV may also occur due to maintain and of normal CO in the animals through haemodilution in by intravenous fluid therapy. Dexmedetomidine is known to preserve blood flow in most vital organs at expense of other non vital organ organs as skin and pancreas (Jena *et al.*, 2014 and Sethi *et al.*, 2017) [22, 52]. However, increase in PCV was also reported during alpha-2 agonists in goats and this increase of PCV was attributed to release of erythrocyte from the reservoir of red blood cells in spleen or production of urine with arousal of shifting mechanism of capillary fluid (Singh *et al.*, 2013). Biermann *et al.* (2012) [5] who reported non-significant decrease in TEC after systemic administration of butorphanol-midazolam combination alone or with ketamine. Mazumdar *et al.* (2012) [33] reported a non-significant decrease in TEC following premedication with dexmedetomidine. However, Mate and Aher (2018) [32] observed that pre-medication with dexmedetomidine-butorphanol combination accompanied by induction and maintenance with propofol significantly reduced TEC. Reduction in erythrocyte values with dexmedetomidine might be due to splenic pooling of erythrocyte and subsequent haemodilution. In group I, there was non-significant increase, while non-significant decrease at different time intervals in group-II animals. There was significant difference between the groups at T1 time interval. Similarly, a decrease in TLC was also reported in diazepam-propofol anaesthesia in canines by Suresha *et al.* (2012) [59]. Jena *et al.* (2014) [22] after pre-medication with dexmedetomidine followed by propofol anaesthesia declined TLC. The decrease in TLC might be due to elevation of adrenaline or nor-adrenaline concentration in peripheral circulation, which depresses proliferative activity of leukocyte. Decline in TLC could also be due to rise in plasma volume due to vascular pooling after anaesthetic administration or confinement of RBC in spleen and lungs (Venugopalan *et al.*, 2002 and Komar *et al.*, 2003) [63, 28]. Similarly, a decreased in total leukocyte count with alpha-2-agonists was reported in canines by Amarpal *et al.* (1998) [3] and in goats by Kumar and Thurmon (1979) [30] and Hugar (1993) [19]. This reduction in total leukocyte count value might be due to splenic dilatation that causes splenic confinement of erythrocyte (Anandmay *et al.*, 2016) [4]. Multiple punctures could also cause vascular damage, *in vivo* platelet aggregation and subsequent *in vitro* platelet aggregation, and a decrease in platelet numbers. (Norman *et al.*, 2001) [38]. These effects could have hampered the observation of thrombocytosis in the studied cats under chemical restraint. Acute stress derived from physical restraint can cause thrombocytosis because epinephrine release causes splenic contraction. (Schafer, 2004) [49]. In both group, non significant increase in the value of neutrophils was observed at pre medication from the base line value afterwards non significant changes were observed. Between the groups there was significant change at the base value. The non-significant increase in neutrophil during observation periods might be related to the anaesthetic and surgical stress that causes activation of adrenal cortex and subsequent production of glucocorticoid that acts on the circulating neutrophils (Solimon *et al.*, 1965) [57] however, butorphanol-acepromazine/ midazolam/ dexmedetomidine might have prevented severe changes resulting from stress that may be the possible reason for non-significant change in DLC. It could be also associated with anesthetic and surgical stress. A similar mechanism might have involved in increasing neutrophils count during the present study which was in accordance to earlier study in dogs (Sharma and Bhardwaj, 2010) [53]. In both the groups, non-significant changes were observed at base line values, after pre medication and at the end of the surgery. In both group, non-significant increase was observed at pre medication from the base line value. Between the groups there were significant difference at P and T1. Significant increase in neutrophils and

significant decrease in lymphocytes was reported with administration of different dose of midazolam in combination with ketamine in dogs (Chandrapuria *et al.,* 2014) [10]. A similar observation of an increase in neutrophils and decrease in lymphocytes was reported after systemic administration of medetomidine-ketamine in caprines (Pawde *et al.,* 1996 and Hugar *et al.,* 1998) [42, 20] and butorphanol-xylazine along with ketamine in canines (Sika, 2013) [54]. Neutrophilia and lymphocytopenia observed in the present study was also in concurrent with the findings of Singh *et al.* (2014). Similar observations have been reported after propofol and xylazine administration (Mukati *et al.,* 2006) [35], midazolam (Butola and Singh, 2003) [8], xylazine, midazolam, propofol and halothane (Cwiek *et al.,* 2009) [14] in dogs. In both the groups, non-significant changes in monocytes, basophils and eosinophils were observed at base line values, after pre medication and at the end of the surgery. Jenna *et al.* (2014) also observed a non-significant elevation in neutrophil, whereas lymphocyte non-significantly declined following pre-medication with dexmedetomidine followed by induction and maintenance with propofol. They also reported non-significant change in monocyte and basophil count as observed in the present study. A variable change in eosinophils and monocytes at different intervals were noticed in all the groups which might be attributed to steroid release provoked by stress due to anaesthesia. Research of the present study are in contradiction to the study Amarpal *et al.* (1998) [3] who observed decline in neutrophil count after pre-medication with α-2 agonists in canines.

Conclusion

From the present study, it was concluded that Midazolam/ Dexmedetomidine anaesthetized with ketamine provide adequate sedation and analgesia in the dogs undergoing elective surgery. Midazolam/ Dexmedetomidine provides better haemodynamic and respiratory stability when used as a pre-anaesthetic for induction with ketamine in the dogs undergoing elective surgery.

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