# Effect of dexmedetomidine with or without butorphanol on the clinico-physiological and haemodynamic stability in dogs undergoing ovariohysterectomy in midazolam and ketamine anaesthesia

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***Abstract***- Clinical anaesthetic trial was conducted in mixed breed dogs undergoing ovariohysterectomy to observe the effect of dexmedetomidine and dexmedetomidine with butorphanol, as adjunct to midazolam and ketamine anaesthesia, on the clinico-physiological and haemodynamic stability in midazolam and ketamine anaesthesia. Atropine (0.04 mg $kg^{-1}$) followed by dexmedetomidine (20µg $kg^{-1}$) after 5 min IM were administered to each animal. Animals were randomised into groups D, DB of eight animals each. In group DB butorphanol (0.1mg kg $^{-1}$) IM was also administered at the time of dexmedetomidine administration. After 10 min of premedication, anaesthesia was induced with midazolam (0.8 mg $kg^{-1}$) IV, in all the groups and maintained with 1% ketamine as and when required. Excellent jaw tone relaxation, abolished palpebral reflex with no significant ($P>0.05$) difference between two groups was observed. Heart rate showed an initial increase followed by a decrease, while respiratory rate decreased below the baseline in all the groups. RT decreased significantly ($P<0.05$) below the baseline. SBP, DBP and MAP increased initially in all the groups and then decreased until 120 min interval. However, mean arterial pressure remained above the baseline throughout the observation period in all the groups. Addition of butorphanol did not have significant effects on the clinico-physiological and haemodynamic stability; however, it reduced the amount of ketamine required for maintenance and better sedation.

***Index Terms***- butorphanol, clinico-physiological, dexmedetomidine, dogs, haemodynamic, midazolam, ovariohysterectomy

## I. Introduction

Dexmedetomidine is a potent and highly selective alpha-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties (Carollo *et al*., 2008; Venn *et al*., 1999) which has been described as a useful and safe adjunct in many clinical applications. It provides a unique "conscious sedation" (patients appear to be asleep, but are readily aroused), analgesia, without respiratory depression. Dexmedetomidine reduces the dose requirements of opioids and anaesthetic agents and attenuates the haemodynamic responses to tracheal intubation and surgical stimuli, besides having organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection and renoprotection (Panzer *et al*., 2009).

Opioids are the most commonly used analgesics to supplement anaesthesia for tolerance of surgical procedures due to their efficacy, rapid onset of action and safety. Butorphanol is an opioid agonist-antagonist with sedative and analgesic properties. It is known to induce mild sedation accompanied by small decreases in arterial blood pressure, heart rate and arterial oxygen tension in dogs. Combinations of butorphanol and alpha-2 adrenoceptor agonists provide reliable and uniform sedation in dogs and cats, although significant decreases in heart and respiratory rates are observed.

Midazolam has modest effects on haemodynamic parameters (Reves *et al*., 1978). Midazolam can be used as a short-acting intravenous induction agent in human beings (Fragen *et al*., 1978; Nilsson *et al*., 2008), owing to its anaesthetic properties i.e. anxiolytic, sedative-hypnogenic, muscle relaxant, and anti-convulsant (Ritcher, 1981), rapid onset of effects and short duration action (Dundee, 1979, Reves *et al*., 1985). Ketamine also provides cardiovascular stability when given with dexmedetomidine butorphanol preanaesthetized dogs. The objective of this study was to compare the effect dexmedetomidine alone dexmedetomidine with butorphanol on the clinico-physiological and haemodynamic stability in dogs undergoing ovariohysterectomy.

## II. Methodology

The study was designed as randomized, blinded, prospective clinical study, with written and informed owner consent. Permission was taken from the Institute Animal Ethics Committee for conducting the clinical trial. 16 healthy mixed breed female dogs undergoing elective ovariohysterectomy were administered atropine (0.04 mg $kg^{-1}$) (Tropine; Neon Laboratories, Palghar, Thane, India) and randomly divided into two groups *viz*. D and DB, each receiving eight animals. In group D, dexmedetomidine (20µg $kg^{-1}$) (Dextomid; Neon Laboratories, Palghar, Thane, India), while in group DB, dexmedetomidine (20µg $kg^{-1}$) and butorphanol (0.1mg kg $^{-1}$) (Butodol; Neon Laboratories, Palghar, Thane, India) were administered IM after 5 min of atropine administration. Ten minutes after the premedication with dexmedetomidine, anaesthesia was induced with midazolam (0.8mg kg $^{-1}$) (Mezolam; Neon Laboratories, Palghar, Thane, India) in all the animals. Anaesthesia was

maintained with 1% ketamine, prepared by diluting 5% with required amount of normal saline (Ketmin 50; Themis Medicare Limited, Uttarakhand, India).

Weak time and down time were recorded as the time elapsed from time of injection of drugs to the time of onset of incoordination/ataxia or drowsiness and till animals attained sternal recumbency, respectively. Recovery time was recorded as the time elapsed from injection of drugs to the appearance of pedal reflex. Sternal recumbency time and complete recovery time was recorded as the time elapsed from the injection of drugs until the animal attainted sternal recumbency, stood and walked unassisted, respectively. Duration of anaesthesia was recorded as the time elapsed from the time of abolition of pedal reflex to the time of reappearance of the pedal reflex. Extubation time was recorded as the time elapsed from successful intubation to reappearance of laryngeal/coughing reflex.

Palpebral reflex; as a measure of depth of sedation and jaw relaxation; as a measure of muscle relaxation were used to monitor the depth of anaesthesia at 0, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min. Extent of salivation was also recorded at the same intervals. Jaw relaxation and palpebral reflexes and salivation score were scored as shown in table 1.

Heart rate (beats $min^{-1}$) (HR) was monitored with non-invasive blood pressure (NIBP) monitor (Surgivet®, Smith's medical PM, Inc. Waukesha, USA) from ulnar or digital artery and respiratory rate (breaths $min^{-1}$) (RR) was measured by counting the excursion of thoraco-abdomen at 0, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min intervals. Rectal temperature was recorded with the help of a digital thermometer. Oxygen saturation of haemoglobin ($SpO_2$) was measured with pulse oxymeter (GIBSON, India). The sensor was applied on the pinna/ tail tip of the animal after clipping hair at the site and cleaning with 70% alcohol (Huss et al., 1995) to record the base value.

**STATISTICAL ANALYSIS**

One way ANOVA was used to compare the means of induction time, intubation time, duration of anesthesia, etc between the groups. Two way ANOVA was used to compare the means/medians at different time intervals among different groups as well as at different time intervals using Proc. GLM of SAS 9.2. The subjective data generated from the scoring of various parameters was analysed using Kruskal Wallis test (Snedecor and Cochran, 1980). Statistical significance was assessed at $p \leq 0.05$.

## III. Results

Mean± SD values of weak, down, duration of anaesthesia, recovery, extubation, sternal recumbency and complete recovery times in different groups are shown in table 2. The loss of pedal reflex was observed at 5.00±3.12 and 4.75±2.92 mins after administration of midazolam. Laryngeal reflex was lost after 5.25 ±2.55, 5.50±1.93 min after administration of midazolam in group D and DB, respectively. Excellent muscle relaxation (fig. 1) was observed from 20 min up to 75 min in group D and up to 60 min in group DB. Thereafter, the muscle tone improved gradually in both the groups. The palpebral reflex (fig. 2) was abolished completely from 20 min up to 75 min in group DB and up to 60 min in group D. Thereafter, the palpebral reflex returned and was mild to moderate till the end of the observation period. There was no significant (P>0.05) difference between two groups in jaw relaxation and palpebral reflex score at any recording intervals. Salivation was normal in all the animals of different groups at different intervals.

Mean± SD values of HR, RR, RT, SBP, DBP and MAP at various time intervals are indicated in fig. 3 to fig. 8. In both the groups, heart rate increased after administration of preanaesthetics and reached the highest value at 15 min interval. Heart rate started decreasing gradually and a significant (P<0.05) decrease was recorded from 75 min onwards as compared to the baseline in group D. In group DB, heart rate increased significantly (P<0.05) at 15 and 20 min. Comparison revealed no significant (P>0.05) differences among the groups except at baseline. Respiratory rate was found significantly below the baseline at 75 min interval in both the groups, however, it was nonsignificantly below the baseline in both the groups at all other intervals l in both the groups. Comparison among the groups revealed no significant (P>0.05) difference in RR at any recording time interval. RT decreased significantly (P<0.05) below the baseline after 30 min in group D and after 20 min in group DB. Systolic blood pressure, diastolic blood pressure and mean arterial pressure increased initially in all the groups and then decreased until 120 min interval. In group D, SBP increased nonsignificantly over the baseline up to 60 min, followed by a nonsignificant decrease below the baseline. DBP increased significantly up to 60 min and thereafter, decreased nonsignificantly below the baseline. MBP decreased after the initial significant (P<0.05) increase up to 30 min and remained nonsignificantly increased during the rest of the observation period. In group DB, SBP, DBP and MBP increased significantly (P<0.05) at 20 min and thereafter, increased nonsignificantly throughout the observation period. MAP remained above the baseline throughout the observation period in all the groups. Comparison among different groups revealed that there was no significant (P>0.05) difference in blood pressure between the groups.

## IV. Discussion

In the animals of group D, the weak time and down time were almost similar to that reported by Amarpal *et al.* (1996), after the administration of medetomidine/dexmedetomidine in dogs and is due to the onset of action of dexmedetomidine has been attributed to its lipophilic property (Amarpal *et al.*, 1996; Singh *et al.*, 2005). Dexmedetomidine, an isomer of medetomidine was also thought to act in a similar way as medetomidine. Butorphanol is also rapidly absorbed after IM administration to dogs and the decrease in weak time in the animals of group DB as compared to that in group D (although nonsignificant) may be attributable to the expected synergistic interaction of butorphanol with dexmedetomidine. The similar down times in groups DB and group D, was in accordance with the study by Jeff *et al.* (2000) where addition of ketamine or butorphanol to the drug regimen did not shorten the onset of lateral recumbency, compared with administration of medetomidine alone. The slightly shorter induction time in group DB than group D could be attributable to additional sedation due to the addition of opioid in preanaesthesia protocol.

Dexmedetomidine causes very mild to mild depression of the laryngeal reflex because of its hypnotic action due to binding to alpha-2 A adrenoreceptors on the cell membrane of neurons of locus coeruleus and opening of inward rectifying potassium channels, resulting in hyperpolarization of membrane, a key element in production of sedation/hypnosis by alpha-2 agonists (Chiu *et al*., 1995). Successfully intubation after midazolam injection suggests that complete depression of laryngeal reflex may be due to synergism between midazolam and dexmedetomidine (Bol *et al*., 2000).

The nonsignificantly shorter duration of anaesthesia and recovery time in group DB can be attributed to lesser amount of ketamine required for maintenance of the anaesthesia in group DB (31.25 mg) than group D (51.25 mg). Longer extubation time was nonsignificantly in group DB than group D may be because of the antitussive property of opioid (Ko *et al.*, 1996). Results of sternal recumbency time in group D supported the observations of Kuusela *et al*. (2000), who reported that dogs administered with dexmedetomidine intravenously at the dose rate of 20µg/kg, were laterally recumbent at 90 min of observation. It has also been reported that dogs given medetomidine and butorphanol regained sternal recumbency after 73.5 ± 19 minutes (Ko *et al*., 1996). Dogs given medetomidine and ketamine were still unable to rise 120 minutes after drug administration (Moens and Fargetton, 1990). Increased sternal recumbancy time in group DB, probably resulted from the synergistic action among dexmedetomidine, butorphanol, midazolam and ketamine, resulting in deeper sedation and reduced metabolic activity to delay redistribution and metabolism of the drugs (Jacobson and Hartsfield, 1993; Ko *et al*., 2000). The increase in standing recovery time with increase in the number of drugs used could be correlated with the increased sedation and decreased metabolic rate in these groups (Jacobson and Hartsfield, 1993; Ko *et al*., 2000). Voluntary urination may be attributed to diuretic effect of alpha-2 agonists due to the interference with the action of antidiuretic hormone on the renal tubular cells and collecting ducts which increase the production of urine (Gellai and Edwards, 1988) and/or to the fluid administration. Urination during the surgery can also be related to the pressure on urinary bladder while manipulating with abdominal cavity. Defecation may be attributed to the loss of anal sphincter tone during anaesthesia.

Sluggish jaw tone after the administration of dexmedetomidine alone or with butorphanol was due to alpha-2 agonist inhibition of alpha-2 adrenoceptors in the interneuron level of spinal cord (Sinclair, 2003). Profound jaw relaxation after midazolam administration can be attributed to the muscle relaxant effect of midazolam which is mediated through glycine receptors in the spinal cord (Ritcher, 1981). Moderate decrease in palpebral reflex observed due to sedation induced by dexmedetomidine (Sabbe *et al*., 1994). Opioid administration increased the score at 20 min in groups DB. This supports the reliable and uniform sedation obtained in butorphanol and alpha-2 adrenoceptor agonist combination (Muir *et al*., 1999 and Ko *et al*., 1996). opioid related additional sedation might be responsible for delayed reappearance palpebral reflex in group DB. Salivation was not observed in any group at any interval of time. It can be attributed to atropine's antimuscarinic effects (Brock, 2001) and α adrenergic receptor mediated action of dexmedetomidine which causes decrease in salivation, decrease in secretions and decrease in bowel motility (Gertler *et al*., 2001).

The significant difference at the baseline in heart rate can be due to the individual variations. Initial increase in HR even after the administration of dexmedetomidine with or without opioid might be attributed to the effect of atropine (Innes and Nickerson, 1975). This is in accordance with the earlier studies in which preemptive administration of atropine was found capable of reversing alpha-2-agonist-induced bradycardia in dogs and caused initial tachycardia (Alibhai *et al.*, 1996). The duration of action of atropine sulphate is only 60 to 90 minutes (Muir, 2007), so the decrease in heart rate recorded after 60 or 70 min may be because of potential effects of alpha-2 agonists and opioids to induce bradycardia (Ko *et al.*, 2000). Bradycardia occurring due to dexmedetomidine is thought to be of parasympathetic origin (Bloor *et al*., 1992). The results of this study also conformed to the observations of Kuusela (2004) who reported decreased HR after dexmedetomidine administration in dogs. It has also been reported that butorphanol facilitates the increase in parasympathetic tone and thereby contributes to bradycardia (Ko *et al.*, 2000). Midazolam is reported to have a non-significant effect on heart rate (Butola and Singh, 2007). So, the effects on the heart rate might be mostly due to dexmedetomidine which were ameliorated by atropine atleast during the first hour of the study. This supports no significant difference between the groups after significant baseline individual variation.

Decrease in RR might be attributed to combined effect of systemic administration of dexmedetomidine, midazolam and ketamine (Sabbe *et al*., 1994, Butola and Singh, 2007 and Wright, 1982), but addition of butorphanol does not have any significant effect on RR. Decrease in rectal temperature after the onset of effect might be attributed to decrease in heat production due to decreased muscular activity and due to direct effect of drugs on hypothalamus (Virtanen, 1989). Decrease in rectal temperature is attributed to the activation of alpha-2 C receptors by dexmedetomidine, which mediate hypothermia (Lemke, 2004) in combination with a reduction in muscular activity and BMR (Ponder and Clarke, 1980; MacDonald *et al*., 1988; Virtanen, 1989). A gradual decrease in rectal temperature following intravenous administration of dexmedetomidine was observed by Raekallio *et al*. (2005); non-significant decrease in RT was also detected in dogs in which midazolam was administered alone (Butola and Singh, 2007). A direct depression of thermoregulatory centre of hypothalamus by ketamine is reported (Wright, 1982). Hypothermia produced by ketamine administration in later stages of the study period might also be due to generalized sedation, reduced metabolic rate, decreased heat production and as a result of general anaesthesia and increased heat loss secondary to cutaneous vasodilation (Lin *et al.*, 1978).

The significant increase in MBP and DBP and nonsignificant increase in SBP after the administration of dexmedetomidine alone or with opoid may be due to high blood concentration of dexmedetomidine and atropine. Anticholinergics are capable of causing hypertension (Alibhai et al. 1996) and high plasma levels dexmedetomidine stimulates alpha-2B adrenoceptors in smooth vessels of blood vessels producing vasoconstriction and consequently hypertension

(MacMillan et al. 1996). The decreases in the BP after significant initial rise may be due to metabolism of dexmedetomidine and resultant low concentrations produce the decrease in blood pressure through alpha-2A stimulation and inhibition of norepinephrine release in autonomic nervous system (MacMillan et al. 1996). Alibhai et al. (1996) has also recorded that medetomidine alone causing a small rise in MAP, which was followed by decrease in the MAP. Midazolam is known to have minimal effects on heart but a significant decrease in arterial pressure has been reported in dogs (Butola and Singh 2007). Midazolam and butorphanol also adds to the decrease in BP after initial rise in this study. Ketamine, on the other hand, produces an increase in cardiac output and heart rate and often produces significant increase in BP (Zielmann et al. 1997). In the present study the overall effect was such that the BP remained either above or nonsignificantly below the base line due to administration of ketamine that combated the expected fall in the BP due to combined action of dexmedetomidine, midazolam and butorphanol.

## V. Conclusion

Dexmedetomidine and dexmedetomidine-butorphanol produced comparable degree of clinico-physiological and haemodynamic stability under midazolam induction and ketamine maintenance anaesthesia in dogs undergoing elective ovariohysterectomy. However, addition of butorphanol for basal anaesthesia reduced the amount of ketamine required for maintenance and better sedation

## Appendix

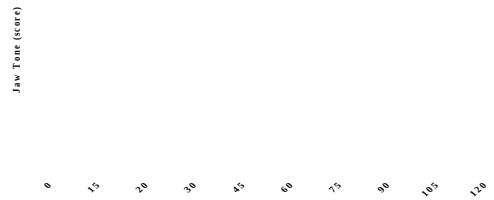


**Figure 1: Median ±SD values (n=16) of score for jaw relaxation in different groups at different time intervals.**




**Figure 2: Median ±SD values (n=16) of score for palpebral reflex in different groups at different time intervals.**

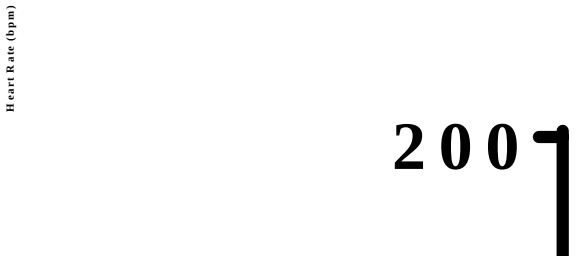


**Figure 3: Mean ±SD values (n=24) of heart rate in different groups at different time intervals. *and ‡ indicates significant (p < 0.05) decrease and # and ¥ indicates significant (p < 0.05) increase from base line value in groups D, DB and DP, respectively. $ indicating significant difference between the groups.**

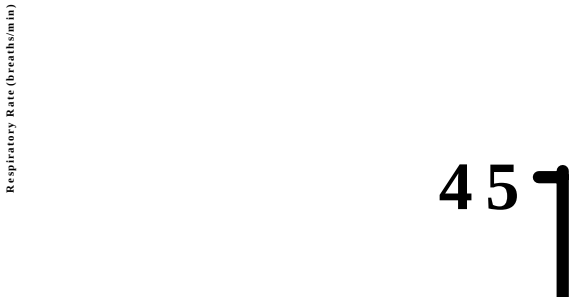


**Figure 4: Mean ±SD values (n=16) of respiratory rate in different groups at different time intervals. *and ‡ indicates significant (p < 0.05) decrease and # and ¥ indicates significant (p < 0.05) increase from base line value in groups D, DB and DP,
respectively.**


**Figure 5: Mean± SD values (n=16) of rectal temperature (°C) in different groups at different time intervals. *and ‡ indicates significant (p < 0.05) decrease and # and ¥ indicates significant (p < 0.05) increase from base line value in groups D, DB and DP, respectively.**

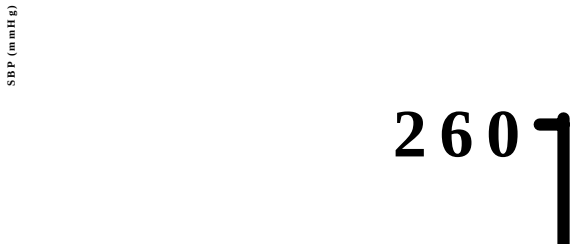


**Figure 6: Mean± SD values (n=24) of systolic blood pressure in different groups at different time intervals. * and ‡ indicates significant (p < 0.05) decrease and # and ¥ indicates significant (p < 0.05) increase from base line value in groups D, DB and DP,respectively.**

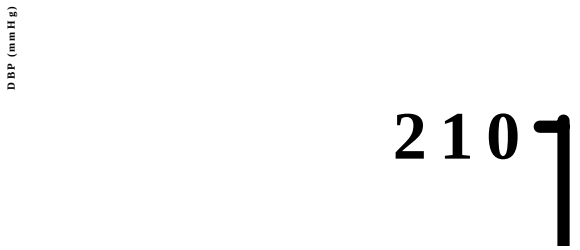


**Figure 7: Mean± SD values (n=24) of diastolic blood pressure (mmHg) in different groups at different time intervals. * and ‡ indicates significant (p < 0.05) decrease and # and ¥ indicates significant (p < 0.05) increase from base line value in groups D, DB and DP, respectively.**

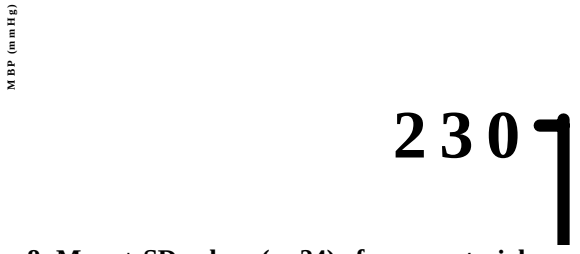


**Figure 8: Mean± SD values (n=24) of mean arterial pressure (mmHg) in different groups at different time intervals. *and ‡ indicates significant (p < 0.05) decrease and # and ¥ indicates significant (p < 0.05) increase from base line value in groups D, DB and DP, respectively**

**Table 1: System of recording of various reflexes and responses used for evaluation of anaesthesia in this study.**

| Score | Parameters | | |
|---|---|---|---|
| | Relaxation of jaw | Palpebral reflex | Salivation |
| 0 | Animal not allowing to open the jaw | Intact and strong (quick blink) | No salivation |
| 1 | Animal resists opening of jaws and closes quickly | Intact but weak (slow response) | Mild salivation |
| 2 | Less resistance to opening the jaws and closed slowly | Very weak (very slow and occasional) | Moderate salivation |
| 3 | No resistance and jaws remain open | Abolished | Excessive salivation |

**Table 2: Median ±SD of induction time, intubation time, duration of anaesthesia, recovery time, extubation, sternal recumbency and complete recovery times in different groups (n=16).**

| Group | D | DB |
|---|---|---|
| Weak Time (min) | 4.38±2.67 | 3.38±2.00 |
| Down time (min) | 4.75±2.38 | 4.75±2.05 |
| Induction time (min) | 5.00±3.12 | 4.75±2.92 |
| Intubation time (min) | 5.25±2.55 | 5.50±1.93 |
| Duration of anaesthesia (min) | 67.38±13.00 | 64.50±17.20 |
| Recovery time (min) | 74.38±12.85 | 68.00±15.33 |
| Extubation time (min) | 69.88±16.92 | 77.00±20.60 |
| Sternal recumbency time (min) | 116.50±12.83 | 118.88±9.89 |

| | | |
|---|---|---|
| Complete recovery time (min) | 169.12±68.66 | 177.00±101.36 |

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