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Evaluation of midazolam as intravenous induction agent for anaesthesia in dogs

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ABSTRACT

A randomized, blinded, clinical study was conducted on 24 healthy mixed breed female dogs to evaluate midazolam as an induction agent for anaesthesia and its effect on vital parameters during elective ovariohysterectomy. Animals were administered atropine and divided randomly into groups D, DB and DP and premedicated with dexmedetomidine, dexmedetomidine and butorphanol, and dexmedetomidine and pentazocine, respectively. After 10 min of premedication, anaesthesia was induced with midazolam (0.8 mg/kg IV), in all the groups and maintained with 1% ketamine as and when needed. Time loss of pedal reflex was considered as the time of induction and it was recorded as 5.00±3.12, 4.75±2.92 and 4.75A±2.66 min in groups D, DB and DP, respectively. Laryngeal reflex was abolished completely, permitting intubation in all the groups. Recovery was smooth and uneventful and recovery time and duration of anaesthesia were comparable in all the groups. Heart rate showed an initial increase followed by a decrease, while respiratory rate decreased below the baseline in all the groups. 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. SpO_2 decreased gradually from the baseline throughout the observation period. The results showed that midazolam at the rate of 0.8 mg/kg IV can be used safely as an induction agent in dogs premedicated with dexmedetomidine alone or with butorphanol or pentazocine while preserving the vital parameters.

Key words: Anaesthesia, Dog, Induction agent, Midazolam, Ovariohysterectomy

Anaesthesia, an indispensable pre-requisite to most of the surgical interventions, help surgeon to perform surgical intervention with maximum precision and sagacity. An ideal anaesthetic agent should produce an appropriate and manageable degree of sedation that is fast in onset, short in duration with uneventful recovery and have minimal influence on cardiovascular, respiratory and other body systems. Furthermore, there should be muscle relaxation and analgesia, no active metabolites and if administered intravenously or intramuscularly, it should have good local tolerance (Lumb and Jones 1984). But the presently available anaesthetics do not satisfy all the requirements of an ideal anaesthetic.

Anaesthesia induced with barbiturates has considerable disadvantages, being known to cause severe tissue reaction, hypotension, respiratory depression, and bronchospasm. Furthermore, when used in conjunction with analgesics, they have an undesirably long and profound sedative effect. Inhalation anaesthetics together with exposure of operating-room personnel to the pollution in the ambient air, require the use of a cumbersome and costly anaesthetic machine, including a suitable breathing system and vaporizer (Matthews 2007). Propofol, another well-known anaesthetic agent, is painful on injection and produces respiratory depression and excitatory effects (involuntary movements, muscle tremors, twitching and coughing). The rapid injection of propofol can result in apnea and, after repeated or continuous propofol dosing, respiratory depression with hypercapnia can occur. Ketamine induces spontaneous movement and, occasionally, convulsions. In short, the search for an ideal anaesthetic agent is still continuing.

According to Fragen *et al.* (1978), midazolam is well suited for use in the setting of anaesthesia owing to its anaesthetic properties i.e. anxiolytic, sedative-hypnogenic, muscle relaxant, and anti-convulsant (Ritcher 1981) and at physiologic pH the benzodiazepine ring of midazolam closes, and it becomes lipid soluble and therefore, CNS-active (Dundee 1979). Moreover, midazolam has modest effects on haemodynamic parameters (Reves *et al.* 1978). The objective of this study was to see the suitability of midazolam as anaesthetic induction agent and to evaluate the effect on clinico-physiological parameters in dogs undergoing ovariohysterectomy. The criteria for induction used were loss of pedal reflex and loss of resistance to opening the mouth fully and loss of response to endotracheal intubation (Muir 2007).

MATERIALS AND METHODS

The study was designed as randomized, blinded,

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prospective clinical study, with written and informed owner consent. Permission was taken from the Institute Animal Ethics Committee for conducting the clinical trial. The sample size was decided by pilot study and resource equation. Healthy mixed breed female dogs (24) weighing 12.29±3.44 kg (mean±SD), undergoing elective ovariohysterectomy were administered atropine (0.04 mg/kg) (Tropine; Neon Laboratories, Palghar, Thane, India) followed by dexmedetomidine (20 µg/kg) (Dextomid; Neon Laboratories, Palghar, Thane, India) after 5 min IM and randomly divided into group D, group DB and group DP, each receiving eight animals. Group D animals did not receive any opoids whereas, groups DB and DP received butorphanol (0.1mg/kg) (Butodol; Neon Laboratories, Palghar, Thane, India) and pentazocine (3 mg/kg) (Roddof; Neon Laboratories, Palghar, Thane, India) IM, respectively. After 10 min of premedication, anaesthesia was induced with midazolam (0.8 mg/kg) (Mezolam; Neon Laboratories, Palghar, Thane, India) in all the animals. The induction dose of midazolam was standardised prior to pilot study as the dose at which pedal reflex was lost. Ketamine (1%) was prepared by diluting 5% with required amount of normal saline (Ketmin 50; Themis Medicare Limited, Uttarakhand, India) and used to maintain anaesthesia. The evaluation of anaesthesia was done on the basis following parameters.

Induction time was recorded as the time elapsed from the time of injection of midazolam until pedal reflex was abolished completely and intubation time until successful intubation. 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; jaw relaxation, as a measure of muscle relaxation and pedal reflex; as a measure of depth of analgesia 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, palpebral and pedal reflexes and salivation score were scored as shown in Table 1.

Heart rate (beats/min) (HR) and systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) were 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) (RR) was measured by counting the excursion of thoraco-abdomen at 0, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min intervals. Oxygen saturation of haemoglobin (SpO_2) was measured with pulse oxymeter (GIBSON, India). The sensor was applied on the pinna of the animal after clipping hair at the site and cleaning with 70% alcohol (Huss *et al.* 1995) to record the base value. The rest of the recordings of SpO_2 were made from the tongue at the same intervals as for MAP.

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. Statistical significance was assessed at $P \leq 0.05$.

RESULTS AND DISCUSSION

Median±SD values of induction time, intubation time, duration of anaesthesia, recovery, extubation, sternal recumbency and complete recovery times in different groups are shown in Table 2. These parameters were comparable in all the groups and did not differ significantly.

Excellent muscle relaxation was observed from 20 min up to 75 min in groups D and DP and up to 60 min in group DB. Thereafter, the muscle tone improved gradually. The palpebral reflex was abolished completely from 20 min up to 75 min in groups DB and DP 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. In all the groups, the pedal reflex became sluggish (intact but very light reflex) after 15 min of administration of dexmedetomidine alone or with butorphanol/pentazocine. The reflex was abolished completely from 20 min up to 75

Table 1. System of recording of various reflexes and responses used for evaluation of anaesthesia

Score	Parameter			
	Relaxation of jaw	Palpebral reflex	Salivation	Pedal reflex
0	Animal not allowing to open the jaw	Intact and strong (quick blink)	No salivation	Intact and strong reflex (strong withdrawal)
1	Animal resists opening of jaws and closes quickly	Intact but weak (slow response)	Mild salivation	Intact but weak reflex (animal responding slowly)
2	Less resistance to opening the jaws and closed slowly	Very weak (very slow and occasional)	Moderate salivation	Intact but very light reflex (slow and occasional response)
3	No resistance and jaws remain open	Abolished	Excessive salivation	Reflex abolished completely

Table 2. Median±standard deviation of durations of anaesthesia phases in 24 female dogs anesthetized with dexmedetomidine-midazolam-ketamine (group D), dexmedetomidine-butorphanol-midazolam-ketamine (group DB), or dexmedetomidine-pentazocine-midazolam-ketamine (group DP) for ovariohysterectomy

Variable	Group		
	D (*n*=8)	DB (*n*=8)	DP (*n*=8)
Induction time (min)	5.00±3.1	4.75±2.9	4.75±2.6
Intubation time (min)	5.25±2.5	5.50±1.9	5.13±2.4
Duration of anaesthesia (min)	67±13	64.50±17	71.00±22
Recovery time (min)	74±12	68±15	73±12
Extubation time (min)	69±16	77±20	84±14
Sternal recumbency time (min)	116±12	118±9	127±24
Complete recovery time (min)	169±68	177±101	180±82

n, number of dogs; Induction time, intubation time and recovery time were recorded as the time elapsed from the time of injection of midazolam until pedal reflex abolished completely, until successful intubation and until reappearance of pedal reflex, respectively; Sternal recumbency time and complete recovery time were recorded as the time elapsed from the injection of dexmedetomidine until the animal attainted sternal recumbency 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.

min in groups D and DB and up to 90 min in group DP. Thereafter, the pedal reflex returned but was weak till the end of the observation period. There was no significant (P>0.05) difference between different groups in jaw relaxation, palpebral and pedal reflex score at various intervals. Salivation was normal in all animals of different groups at different intervals. The total amount (mean±SD) of ketamine needed to maintain the state of surgical anaesthesia in groups D, DB and DP were 63.75±9.25, 81.25±68.96 and 76.87 ±63.41 mg without any significant difference between the groups.

Surgical anaesthesia is characterised by analgesia, sedation and muscle relaxation, which was met in the present study as indicated complete loss of pedal reflex, loss of palpebral reflex and loss of resistance to opening the mouth fully and laryngeal response, respectively. This can be due to combined effect of dexmedetomidine and an increased dose of midazolam IV. Dexmedetomidine alone at the rate of 20 µg/kg IV has been reported to produce only sedation and not anaesthesia (Kuusela *et al.* 2004). Midazolam, on the the hand, has been proven to induce surgical anaesthesia (Alison *et al.* 1982). Dexmedetomidine causes very mild to mild depression of the laryngeal reflex probably due to its hypnotic action by binding to α_2-Aadrenoreceptors in locus coeruleus, resulting in hyperpolarization of membrane (Chiu *et al.* 1995, Jeff *et al.* 2000). The complete depression of laryngeal reflex after administration of midazolam may be due to synergism between midazolam and dexmedetomidine (Bol *et al.* 2000). The administration of increased dose of midazolam intravenously, produces sufficient sedation, muscle relaxation and analgesia to be used as induction agent in animals preanaesthetised with dexmedetomidine.

The animals were continuously monitored and maintained in surgical anaesthesia throughout the surgery (53±9.14 min). Delayed reappearance of pedal reflex after completion of surgery might be due to the effect of ketamine. Slightly longer time of extubation in the animals of groups DP and DB than group D could be due to antitussive property of opioid (Ko *et al.* 1996). Prolonged sternal recumbency and complete recovery time recorded in all groups supported the observations of Kuusela *et al.* (2000), who reported that dogs administered with dexmedetomidine intravenously at the dose rate of 20 µg/kg, were laterally recumbent at least up to 90 min. Ko *et al.* (1996) reported recumbency time of 73.5±19 min in dogs given medetomidine and butorphanol. Slightly longer recumbency/righting reflex, complete recovery time in groups DB and DP probably resulted from the synergistic action among dexmedetomidine, butorphanol/pentazocine, midazolam and ketamine, resulting in deeper sedation and reduced metabolic activity to delay redistribution and metabolism of the drugs (Ko *et al.* 2000).

Sluggish jaw tone after the administration of dexmedetomidine alone or with butorphanol/pentazocine 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 (Ritcher1981). Palpebral reflex becomes sluggish in all species when surgical anaesthesia is attained. 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 and DP. This supports the reliable and uniform sedation obtained in butorphanol and alpha-2 adrenoceptor agonist combination (Muir *et al.* 1999, Ko *et al.* 1996). However, complete loss of the palpebral reflex was observed only after midazolam administration due it's hypnotic action related to modulation of GABA channel activity by occupation of benzodiazepine receptors, leading to GABA accumulation (Reves *et al.*1985). Opioid related additional sedation might be responsible for delayed reappearance palpebral reflex in groups DP and DB. It has been reported that assessment of sedation by evaluation of palpebral reflex may be less relevant in dogs not induced for general anaesthesia (Leppanen *et al.* 2006), however, in the present study evaluation of palpebral reflex provided a fair idea of the depth of sedation and it was possible to differentiate between mild, moderate and deep sedation.

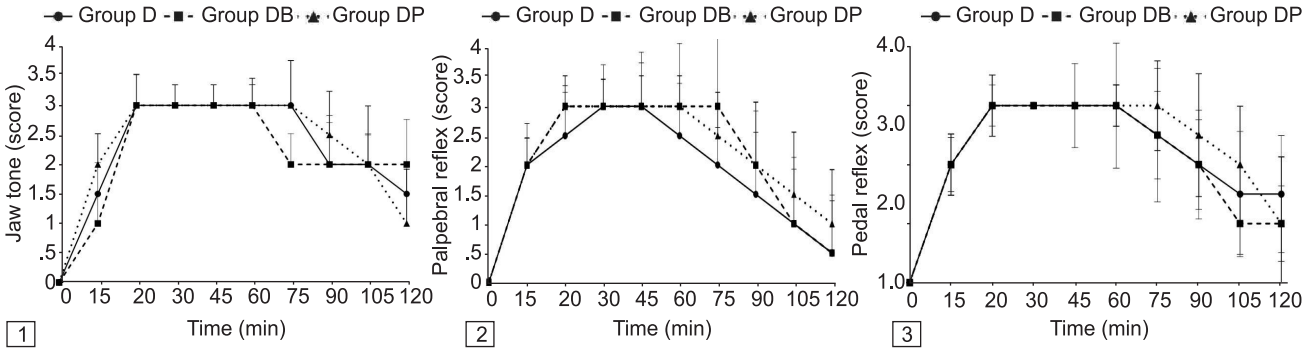
The pedal reflex is a useful guide to the depth of analgesia

and anaesthesia in dogs and is lost completely at the transition from light to medium surgical anaesthesia. The increased pedal reflex scores reflects the increased state of analgesia due to effects of dexmedetomidine or dexmedetomidine-butorphanol/pentazocine combination before induction of anaesthesia. Alpha-2 adrenoceptor agonists significantly elevate the nociceptive threshold mediated by alpha-2 adrenoceptors in the dorsal horn of the spinal cord (Sullivan *et al.* 1992). Butorphanol is a central-acting analgesic which ameliorates the signs of superficial and visceral pain (Muir and Robertson 1985). Furthermore, medetomidine potentiates the antinociceptive action of opioid agonist-antagonist like butorphanol due to interaction between opioid and alpha-2 adrenoceptors in the spinal cord (Ossipov *et al.* 1990). Pentazocine via both MORs and KORs can contribute to antinociceptive effects to somatic as well as visceral pain (Bidlack *et al.* 2000). The maximal score attained at 20 min reflects state of surgical anaesthesia and could be attributed to midazolam. Midazolam is reported to have a considerable effect on the nociceptive transmission in superficial dorsal horn (Kohno *et al.* 2006). Alison *et al.* (1982) has reported midazolam induces anaesthesia in human beings and can be a suitable alternative to thiopental for induction and maintenance of anaesthesia for elective caesarean section (Crawford *et al.* 1989). The loss of pedal reflex was maintained by combined effect of preanaesthetics, midazolam and ketamine. The reflexes did not return to normal even till two hours of study consistent with the observation of Kinjavdekar *et al.* (2000) who reported that medetomidine produces longer duration (90– 105 min) of mild to moderate analgesia of hind quarter, flank and thorax in goats.

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).

Physiological and haemodynamic observations: Mean±SD values of HR, RR, SBP, DBP, MAP and SpO_2 in different groups at various time intervals are shown in Figs. 4–9. In all the groups, heart rate increased after administration of preanaesthetics and reached the highest value at 15 min interval. In group DB, heart rate increased significantly (P<0.05) at 15 and 20 min. 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).

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 DP, the HR decreased significantly (P<0.05) below the baseline at 120 min interval only. Comparison among the groups revealed no significant (P>0.05) differences among different groups except between groups D and DB at baseline. The duration of action of atropine sulphate is only 60 to 90 min (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). Pentazocine is reported to have minimal cardiovascular and mild respiratory depressant actions in animals (Lumb and Jones 1984). Midazolam is reported to have a non-significant effect on heart rate (Butola and Singh 2007). So, the effects on the heart rate were mostly due to dexmedetomidine which were ameliorated by atropine



Figs 1–3. **1.** Median±SD values (n=24) of score for jaw relaxation 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. **2.** Median±SD values (n=24) of score for palpebral reflex 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. **3.** Median±SD values (n=24) of score for pedal reflex 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.

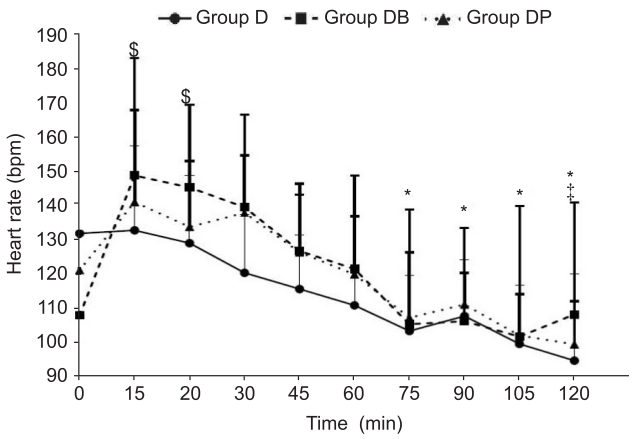


Fig. 4. Mean±SD values (n=24) of heart rate in different groups at different time intervals. *, † and ‡ indicate significant (P<0.05) decrease and #, $ and ¥ indicate significant (P<0.05) increase from base line value in groups D, DB and DP, respectively.

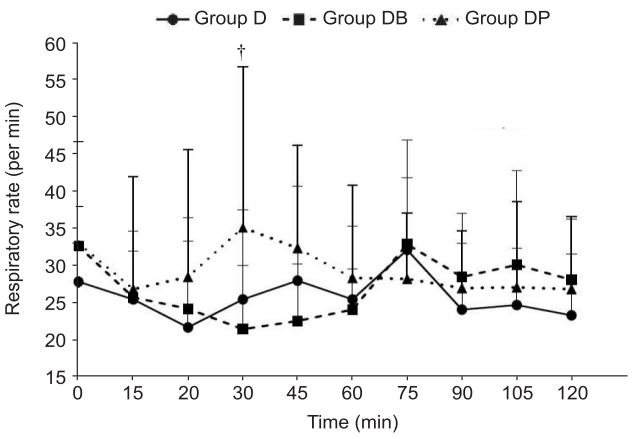


Fig. 5. Mean±SD values (n=24) of respiratory rate in different groups at different time intervals. *, † and ‡ indicate significant (P<0.05) decrease from base line value in groups D, DB and DP, respectively.

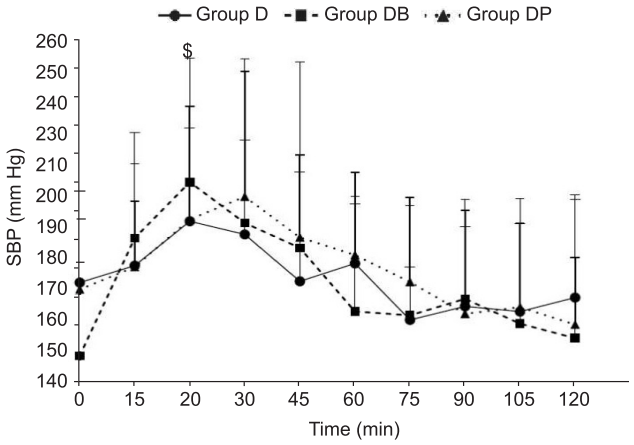


Fig. 6. Mean±SD values (n=24) of systolic blood pressure in different groups at different time intervals. *, † and ‡ indicate significant (P<0.05) decrease and #, $ and ¥ indicate significant (P<0.05) increase from base line value in groups D, DB and DP, respectively.

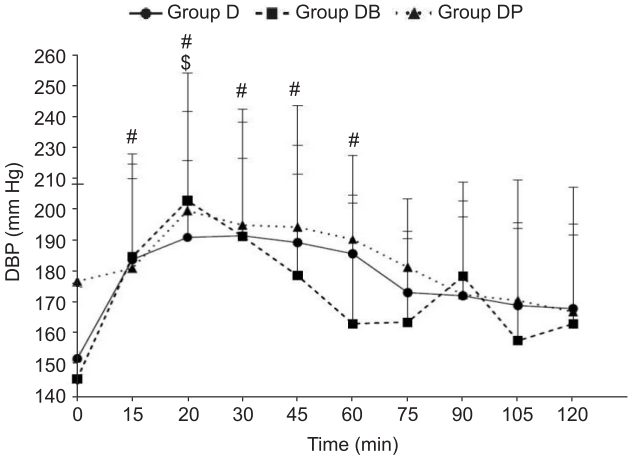


Fig. 7. Mean±SD values (n=24) of diastolic blood pressure (mm Hg) in different groups at different time intervals. *, † and ‡ indicate significant (P<0.05) decrease and #, $ and ¥ indicate significant (P<0.05) increase from base line value in groups D, DB and DP, respectively.

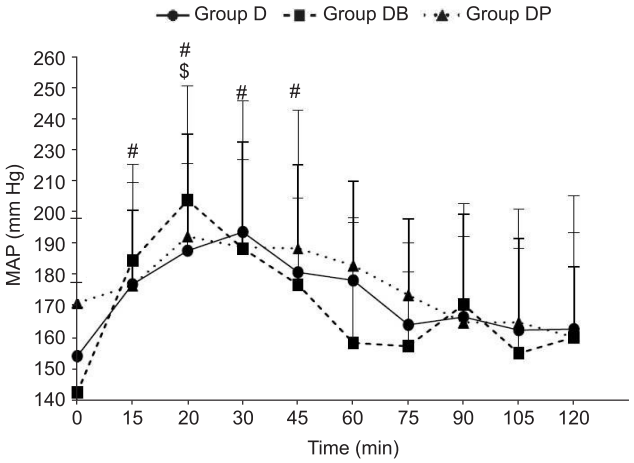


Fig. 8. Mean±SD values (n=24) of mean arterial pressure (mm Hg) in different groups at different time intervals. *, † and ‡ indicates significant (P<0.05) decrease and #, $ and ¥ indicate significant (P<0.05) increase from base line value in groups D, DB and DP, respectively.

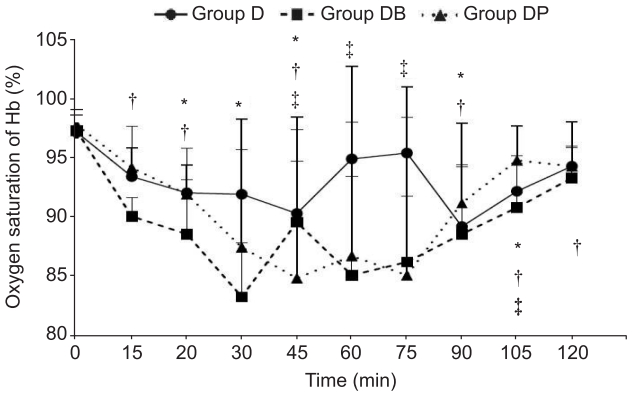


Fig. 9. Mean±SD values (n=24) of oxygen saturation (SpO_2%) in different groups at different time intervals. *, † and ‡ indicate significant (P<0.05) decrease and #, $ and ¥ indicate significant (P<0.05) increase from base line value in groups D, DB and DP, respectively.

atleast during the first hour of the study and supported by no significant difference between the groups after significant baseline individual variation.

Respiratory rate decreased nonsignificantly below the baseline in all the groups at all intervals except at 75 min interval in groups D and DB and at 30 min in group DP. Comparison among the groups revealed no significant (P>0.05) difference in RR at different time intervals. Decrease in RR might be attributed to combined effect of systemic administration of dexmedetomidine and midazolam (Sabbe *et al.* 1994, Butola and Singh 2007). Oyamada *et al.* (1998) opined that inhibition of locus coeruleus neurons by activation of alpha-2 adrenergic pathway may be responsible for alpha-2 agonists induced RR depression. Midazolam also causes decrease in respiratory rate (Butola and Singh 2007). Ketamine is also known to have dose dependent depressant effect on respiratory system (Wright 1982).

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. 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). 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 MAP increased significantly (P<0.05) at 20 min and thereafter, increased nonsignificantly throughout the observation period. In group DP; SBP, DBP and MAP increased nonsignificantly up to 75 min and thereafter, decreased nonsignificantly from the baseline value. 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 MAP between the groups. The decrease in 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 caused 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 was reported in dogs (Butola and Singh 2007). Midazolam and butorphanol/pentazocine 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/ pentazocine.

SpO_2 decreased gradually from the baseline throughout the observation period in all the groups. In group D, there was a significant (P<0.05) decrease in SpO_2 at 20, 30, 45, 90 and 105 min intervals. In group DB, SpO_2 decreased significantly (P<0.05) at all intervals as compared to the baseline except at 120 min interval where as in the group DP, SpO_2 was recorded below the base line throughout the course of the study but significantly (P<0.05) only at 45, 60 and 75 min. In group DB, SPO_2 was significantly (P<0.05) lower at 15 min as compared to groups D and DP; and at 105 min as compared to group DP. Low SpO_2 is indicative of reduced arterial oxygenation and diminished tissue perfusion. Low arterial oxygen concentration could be due to vasoconstriction and respiratory depression due to sedation (Leppanen *et al.* 2006). Dexmedetomidine causes vasoconstriction (Kuusela *et al.* 2000). The decrease in SpO_2 in the present study was in accordance with the findings of Dere *et al.* (2010). More decrease in RR in group DB than in other two groups could be the plausible reason for significantly more decrease initially and less elevation towards the end of the study in SpO_2 in group DB.

In conclusion, Midazolam at the rate of 0.8 mg/kg IV can be used as an induction agent in dogs premedicated with dexmedetomidine alone or with butorphanol or pentazocine while keeping heart rate, blood pressure and respiratory rate in normal range. However, a significant decrease in SPO_2 was recorded.

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