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# Evaluation of Clinico-physiological Effects of Ketamine Alone and in Combination with Dexmedetomidine or Butorphanol in Atropinized Dogs

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## ABSTRACT

**Background:** Ketamine is rarely used alone because of its association with poor muscle relaxation, tachycardia, catalepsy or muscle rigidity and therefore commonly used in combination with alpha 2 agonist or opioid to minimize the untoward effects. The aim of the present anaesthetic study was to evaluate the clinico-physiological effects of ketamine alone and in combination with dexmedetomidine or butorphanol for inducing adequate anaesthesia in dogs.

**Methods:** The present anaesthetic study was conducted on 18 (eighteen) healthy dogs of either sex and randomly divided into three groups (K, DK and BK) with six animals in each group. Atropine sulphate @ 0.04 mg/ kg was administered intramuscularly 15 minutes prior to anaesthetic study to all the animals. In group K, ketamine HCl alone was administered @ 5 mg/kg by slow i/v and kept as control. In group DK and BK, after administration of atropine sulphate 15 minutes later dexmedetomidine @ 10 µg/kg i/m and butorphanol @ 0.2 mg/kg i/m were administered respectively. Ten minutes later ketamine HCl was administered @ 5 mg/kg slowly intravenously in both group DK and BK to induce surgical stage of general anaesthesia. The following clinical parameters were recorded *viz*., onset of sedation, onset of anaesthesia, degree of analgesia, extent of muscle relaxation, duration of anaesthesia and complete recovery. The physiological parameters (rectal temperature, heart rate and respiratory rate) were recorded before anaesthetic study at 0 min. and at 10 minutes after preanaesthetic administration and then at 10, 20, 40, 60, 90, 120 and 180 minutes after ketamine anaesthesia. All the data were analyzed using SPSS v 15.0 statistics software program and presented as mean±Standard Error.

**Result:** The onset of sedation was quicker in group DK followed by group K and BK. Duration of anaesthesia and complete recovery in group DK was significantly ($p<0.01$) longer than in group K and BK. The degree of analgesia was excellent in group DK and good in group K and BK. The extent of muscle relaxation was excellent in group DK, good in group BK and was poor in group K. The physiological parameters showed transient changes which compensated and remained within normal range during the observation period. The above anaesthetic study suggests that ketamine in combination with dexmedetomidine or butorphanol can be safely used for inducing adequate anaesthesia in dogs. However, dexmedetomidine-ketamine can be used safely for longer duration of surgical procedures in dogs.

**Key word:** Anaesthesia, Atropinized dog, Butorphanol, Dexmedetomidine, Ketamine.

## INTRODUCTION

Balanced anaesthesia for successful surgical procedures is attained when two or more drugs are combined with the aim to achieve desirable hypnosis, analgesia and muscle relaxation. However, there is no anaesthetic drug available till date that can provide desirable anaesthesia by itself. Therefore, combination of sedatives and other anaesthetics has been widely used in animal practice to attain desirable effects of general anaesthesia. For this purpose, commonest drugs used are ketamine, dexmedetomidine, butorphanol and atropine sulphate. Ketamine is a non-competitive N-methyl-d-aspartate receptor antagonist which produces profound analgesia without muscle relaxation that is characterized by catatonic and amnesia with or without actual loss of consciousness (Hall and Clarke, 1990). Ketamine possibly increases muscle tone and induces spontaneous movement and occasionally, convulsions. Recovery from ketamine anaesthesia is often associated with hyperexcitability. To reduce these undesirable effects, it is often used in conjunction with alpha-2 agonist like dexmedetomidine and potent opioids agonist like butorphanol. Atropine, an anticholinergic agent, blocks muscarinic receptors at the postganglionic terminations of

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cholinergic fibers in the autonomic nervous system. Atropine has been used to prevent bradycardia caused by administration of alpha 2 agoinsts in dogs (Ko *et al*., 2001). Dexmedetomidine is an active optical enantiomer isolated from the racemic compound medetomidine and has been shown to have most of the potent sedative and analgesic effects of the parent drug (Congdon *et al*., 2011). Dexmedetomidine is as safe and effective as medetomidine when administered at equipotent dose (half the medetomidine dose) (Kuusela *et al*., 2001). 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 a parenteral synthetic opioid agonist-antagonist analgesic of the nalorphanecyclozocine class. Its analgesic potency is 3-5 times that of morphine but chemical structure is similar to morphine. Butorphanol is known to induce mild sedation accompanied by small decreases in arterial blood pressure, heart rate and arterial oxygen tension. Review reveals very scanty literature on the use of dexmedetomidine or butorphanol and its combination with ketamine in dog. The objective of this anaesthetic study was to evaluate the clinico-physiological effects of ketamine alone and in combination with dexmedetomidine or butorphanol in dogs for inducing adequate anaesthesia in dogs. The effort behind this study was to maximize the desired effects of anaesthestic agent and minimize their side effects.

## MATERIALS AND METHODS

### Selection of animals

The present anaesthetic study was conducted during January 2013 to July 2013 at Department of Veterinary Surgery and Radiology, College of Veterinary Science and A.H., Anjora, Durg (C.G.) on 18 (eighteen) healthy dogs of either sex weighing between 10 to 20 kg body weight. They were randomly divided into three groups *viz*., group K, DK and BK, comprising of 6 animals in each.

### Preparation of animals

All dogs were dewormed with Praziplus (Albendazole 300 mg with Praziquantel 25 mg) Tab. @ 1 Tab. / 10 kg body weight orally fifteen days before the start of anesthetic study. The animals were fasted overnight and drinking water was withheld for 6 hours before the administration of anaesthesia. The animals were kept under uniform feeding and managemental practices throughout the study period. All the animals were subjected to clinical examination before the start of anaesthetic study and the base values (0 min.) for physiological parameters were recorded as reference.

### Anaesthetic protocols

All the 18 animals were divided randomly into three groups designated as group K, DK and BK with six animals in each group. The animals of all the three groups were administered with atropine sulphate @ 0.04 mg/ kg intramuscularly 15 minutes prior to anaesthetic study. The animals of group K received ketamine HCl alone @ 5 mg/kg by slow intravenous injection and kept as control group. In group DK and BK, after administration of atropine sulphate, 15 minutes later dexmedetomidine @ 10 µg/kg i/m and butorphanol @ 0.2 mg/kg i/m were administered respectively. Onset of sedation and recumbency was recorded after administration of preanaesthetic drugs (dexmedetomidine /butorphanol) in group DK and BK. Ten minutes later ketamine HCl was administered @ 5 mg/kg slowly intravenously in both group DK and BK to induce surgical stage of general anaesthesia.

### Clinical parameters

The following clinical parameters were assessed after ketamine administration *viz*., onset of anaesthesia, degree of analgesia, extent of muscle relaxation, duration of anaesthesia and complete recovery. Onset of anaesthesia was recorded as time elapsed from injection of drugs to abolition of pedal reflex. Degree of analgesia was recorded by presence or absence of pedal reflex, pinprick, palpebral, corneal, conjunctival reflexes. Palpebral reflex was noted by tapping the skin at the medial canthus of the eye or turning the finger along the eye lashes while the pedal reflex was noted by the pinching the interdigital web of hindfoot of dog. To assess the corneal reflex, a gentle palpation of the lateral aspect of cornea was done. A reflex on a gentle prick of an inoculation needle on the medial aspect of the thigh was indicative of pinprick reflex. Extent of muscle relaxation was recorded by observing the tone of jaw muscles, flaccidity of tongue and relaxation of anal sphincter and it was graded as poor, good and excellent. Relaxation of jaw was recorded by observing the resistance to opening of jaw while pulling the jaw apart. Duration of anaesthesia was recorded as the time taken elapsed from the onset of anaesthesia, i.e. time of abolition of pedal reflex to the time of reappearance of pedal reflexes in the anaesthetized animal. Complete recovery was recorded as the time elapsed from administration of drug to the time of standing and walking unassisted. Any complications observed during and after anaesthesia in all the animals *viz*. nausea, vomiting, salivation, lacrimation, muscle twitching etc. were noted.

### Physiological parameters

The physiological parameters included rectal temperature, heart rate and respiratory rate which were recorded before anaesthetic study at 0 min. and at 10 minutes after preanaesthetic administration and then at 10, 20, 40, 60, 90, 120 and 180 minutes after ketamine anaesthesia.

### Statistical analysis

The mean and standard error of the recorded values were calculated and data was analyzed using Analysis of Variance (ANOVA). It was further analyzed using SPSS v 15.0 statistics software program and presented as mean±Standard Error.

## RESULTS AND DISCUSSION

### Clinical parameters

#### (a) Onset of sedation and recumbency

In group DK, there was marked sedation with lowering of head after dexmedetomidine administration within 4.30±1.33 min. All the animals attained lateral recumbency in 5.25±1.05 min. remained conscious but were unable to stand when disturbed. Mild sedation was observed in group BK within 7.35±1.56 min. after butorphanol administration and animal went to lateral recumbency in 8.37±1.87 min. whereas in group K, animal did not show any signs of sedation and recumbency. In the present study, onset of sedation and recumbency was earlier in DK group than other group, due to onset of action of dexmedetomidine owing to its lipophilic property (Amarpal *et al*., 1996). Ahmad *et al.* (2013) reported onset of sedation at 4.50±0.96 minutes after intramuscular injection of dexmedetomidine in dogs. In group DK, there was very good sedation when compared to group K and BK. The sedative/hypnotic effects of dexmedetomidine are mediated through pertussis-sensitive inhibitory G protein in locus coeruleus resulting in hyperpolarization and reduced nerve conduction (Kuusela *et al.*, 2000). Similar observations were also recorded by Alvaides *et al.* (2008) after using the combination of dexmedetomidine (10 µg/kg) with acepromazine (0.05 mg/kg) as premedicants to ketamine anaesthesia in dogs.

#### (b) Onset of anaesthesia

The onset of anaesthesia was at 0.98±0.02 min., 0.92±0.01 min. and 1.01±0.01 min. in group K, DK and BK respectively after ketamine administration. All the animals of three groups showed marked sedation and lateral recumbency. The shorter onset of anaesthesia observed in group DK might be due to effects of dexmedetomidine which produced sufficient degree of sedation prior to induction with ketamine. The anaesthetic action of ketamine is produced by interruption of ascending transmission from those parts of the brain responsible for unconscious and conscious functions so it possesses potent analgesic property. In this study, the corneal reflex remained unchanged throughout the anaesthesia in all the three groups. Similarly, Pandey and Vijayvargiya (1996) documented that after induction with ketamine, the palpebral and corneal reflexes remain present throughout the anaesthesia. Animals of group K (Ketamine) showed no sign of excitement and sedation with protrusion of tongue from buccal cavity after onset of anaesthesia. The anal pinch reflexes were sluggish but not fully abolished. The muscle relaxation was poor and rigidity of limb was noticed in all the animals which might be due to stimulation of central adrenergic receptors (Usha and Rajagopalan, 1990). In group DK (Dexmedetomidine-Ketamine) animals, the induction was smooth and with no sign of excitement and marked sedation with protrusion of tongue from buccal cavity after onset of anaesthesia. In the present study, dexmedetomidine helped in producing short onset of anaesthesia in group DK with complete absence of anal pinch reflexes. Dexmedetomidine caused mild depression of the laryngeal reflex because of its hypnotic action due to binding of alpha 2 adrenoreceptor on the cell membrane of neurons of locus coeruleus (Chiu *et al.,* 1995). In group BK (Butorphanol-Ketamine) animals, the induction was smooth along with sedation and protrusion of tongue from buccal cavity after onset of anaesthesia. The anal pinch reflexes were abolished completely. Therefore, in the present study, ketamine was combined with alpha-2 agonist dexmedetomidine and potent opioids agonist butorphanol to overcome side effects as ketamine alone has a poor muscle relaxant property.

#### (c) Presence or absence of various reflexes

Corneal, conjunctival and palpebral reflexes were present in all the three groups but were sluggish in group DK animals as compared to group K and BK animals. Pedal reflexes were abolished and anal sphincter was relaxed in group DK and BK while in group K, anal sphincter was not relaxed completely during anaesthesia. Moderate decrease in palpebral reflex observed in group DK could be due to sedation induced by dexmedetomidine. Similar findings were reported by Sabbe *et al*. (1994).

#### (d) Extent of muscle relaxation

Excellent muscle relaxation was observed in group DK which was sufficient to perform major surgical procedures as compared to group K and BK. This might be due to dexmedetomidine as alpha 2 agonists are known to produce good muscle relaxation (Lemke, 2007) which is attributed to inhibition of intraneuronal transmission of impulses by alpha 2 agonist at the level of CNS. In group K, the extent of muscle relaxation was poor where ketamine was administered alone and there was muscle rigidity which might be due to stimulation of central adrenergic receptors.

#### (e) Extent of Jaw relaxation

Jaw relaxation signified the extent of muscle relaxation in all the groups. Jaw tone was significantly ($p<0.01$) reduced in group DK as compared to group K and BK. In group K, it was rigid to open jaw while in group BK jaw was partially opened when traction was given in opposite direction in upper and lower jaw. As ketamine does not possess muscle relaxant property therefore relaxation of jaw in group DK might be attributed to the action of dexmedetomidine.

#### (f) Degree of analgesia

In all the three groups, the degree of analgesia was excellent as there was no pain sensation on needle pricking but it persisted for longer period in group DK. 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 reduces spinal reflexes (Talukder and Hikas, 2009). Dexmedetomidine activates alpha 2 adrenergic receptors reducing the transmission of nociceptive signals like substance P (Bekker and Sturaitis, 2005). Butorphanol

is also rapidly absorbed after intramuscular administration in dogs and has strong agonist activity at the kappa and sigma receptors to produce its analgesic effect. Butorphanol 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). Ketamine has been reported to possess analgesic properties. It inhibits ion channels at the membrane levels and acts on the opioid receptor to exhibit antinociceptive effects (Demirkan *et al*., 2002).

**(g) Duration of Anaesthesia**

The mean duration of anaesthesia in group DK was significantly ($p<0.01$) longer (49.17±2.93 min.) than in group K (10.69±0.30 min.) and group BK (19.00±0.47 min.). Longer duration of anaesthesia in animals of group DK and BK might be due to synergistic action of dexmedetomidine and butorphanol with ketamine respectively. In the above study, the highest duration of anaesthesia was observed in animals of group DK as compared to group BK and K. This might be due to wide distribution of dexmedetomidine and ketamine in the body because they are highly soluble in lipid and can get redistributed into muscles and adipose tissue. However, administration of butorphanol in group BK resulted in slight increase in the duration of anaesthesia. Moens and Fargetton (1990) also reported longer duration of anaesthesia after administration of medetomidine @ 40ìg/kg combined with ketamine @ 5mg/kg. The quality of anaesthesia and extent of muscle relaxation was excellent in group DK to perform major surgical procedures. In group K and BK, short surgical anaesthesia was achieved and was suitable for surgical procedures of short duration. Ubrahim *et al.* (2002) also documented satisfactory anaesthesia of 20 to 25 mins. duration after administration of ketamine-butorphanol combination in dogs. Ketamine itself is a short acting drug, but its relatively longer duration of anaesthesia in the present study in group DK could be attributed to the action of dexmedetomidine administered as preanaesthetic.

**(h) Complete recovery**

The time taken for complete recovery from anaesthesia was significantly ($p<0.01$) more in group DK (90.50 ±3.50 min.) as compared to group K (37.92±1.42 min) and group BK (53.33±2.17 min). The recovery was smooth, free from excitement and uncomplicated in group DK. However, in group K, muscular rigidity and excitement was reported where ketamine was used alone. Similarly, Lin (2007) also reported that ketamine when used alone for anaesthesia in dogs produces spontaneous movement, muscle rigidity and violent recovery. In group BK, involuntary limb movement, howling and coughing in three animals was reported at the time of recovery which might be due to antitussive property of butorphanol. Preanaesthetic administration of dexmedetomidine in group DK and butorphanol in group BK prolonged the recovery time which might be due to depressant action of these preanaesthetics on central nervous system. The result of this study was in agreement with the findings of Bhat *et al.* (2001) in canines. Dogs given medetomidine and ketamine were still unable to rise 120 minutes after administration (Moens and Fargetton, 1990). However, dexmedetomidine was administered as preanaesthetic in group DK producing deeper sedation which might have led to reduced metabolic activity with delay redistribution and metabolism of the drugs, resulting in prolongation of recovery time (Ko *et al*., 2000). In the present study, smooth recovery was observed in group DK and BK which might be attributed to combined effect of preanaesthetic and ketamine.

**(i) Complications**

In group K, there were muscular tremors and stiffness in the limbs soon after onset of anaesthesia, this is known as catalepsy in which eye remains open but extremities gets paralyzed and animal remain unaware of its surroundings. This might be due to action of ketamine on limbic system and stimulation of central adrenergic receptors. Similar findings have been observed by Haskins *et al.,* (1985) after ketamine anaesthesia in dogs. In group BK, involuntary limb movement, howling and coughing in three animals were reported at the time of recovery which might be due to antitussive property of butorphanol. Manifestations of excitement included vocalization, violent paddling movements, opisthotonus and periodic rigidity of one or more limbs were recorded in the course of butorphanol-ketamine anaesthesia. No complication was recorded in animals of group DK because of dexmedetomidine and ketamine as both are complimentary to each other for potentiating the analgesia and minimizing the side effects to produce balanced anaesthesia.

**Physiological parameters**

**(a) Rectal temperature (ºF)**

In group K, a non significant decrease in rectal temperature was recorded up to 10 min. following ketamine administration with further non-significant increase upto 60 min., thereafter the values returned to the base line at 90 min. This might be due to direct depression of thermoregulatory centre of hypothalamus by ketamine as reported by Wright (1982). A non-significant increase in rectal temperature at 60 minutes after ketamine anaesthesia could be attributed to increased tonicity of muscles. Similar findings have been reported by Haskin *et al*. (1985) after ketamine anaesthesia in dogs. Rectal temperature decreased significantly ($p<0.01$) at 10 min. after premedication with dexmedetomidine in group DK. However, after induction with ketamine, rectal temperature continued to decrease significantly ($p<0.05$) between 20 to 60 mins. with a peak decrease at 40 min and with gradual increase towards normalcy upto 180 min. of observation period as shown Fig 1. Decrease in rectal temperature is

attributed to the activation of alpha 2 C receptors by dexmedetomidine, which mediate hypothermia (Lemke, 2004) in combination with reduction in muscular activity and BMR. In the present study, the decrease in rectal temperature might be due to depression of the thermoregulatory centre or basal metabolic rate or reduction in peripheral circulation and muscle relaxation (Ahmad *et al.,* 2013). In group BK, there was non-significant decrease in the rectal temperature upto 60 min. after ketamine administration and values returned to pre-administered level by 180 min. The reduction in rectal temperature could be attributed to decreased metabolic rate, depressed peripheral circulation and depression of thermoregulatory centers. However, in the present study, rectal temperature in all the three groups began to decrease after ketamine anaesthesia but returned to normal physiological range after recovery.

**(b) Heart rate (beats per minute)**

Heart rate increased gradually after administration of atropine sulphate in group K with a significantly ($p<0.05$) increase at 20 min. after ketamine alone which decreased gradually towards pre-administration level by 180 min as compared to base value. Initial increase in heart rate in group K might be attributed to the effect of atropine due to preemptive administration which potentiated the cardiac stimulatory effect of ketamine leading to rise in heart rate. Ketamine stimulates the cardiovascular system resulting in increased heart rate principally through the sympathetic

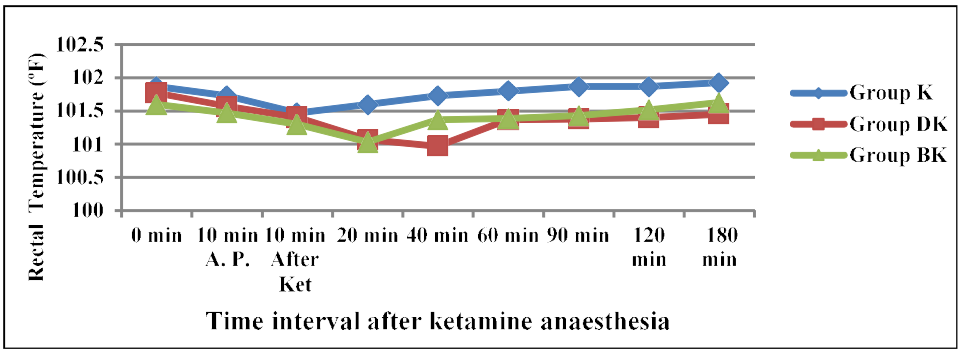


**Fig 1:** Effect on rectal temperature in different group at various time intervals in atropinized dogs

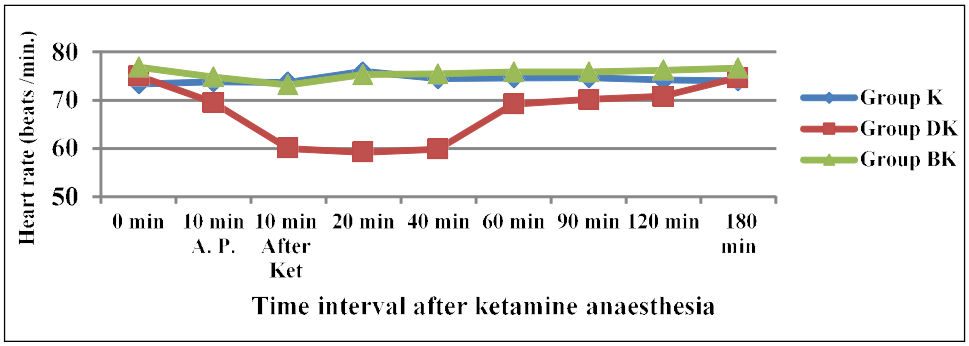


**Fig 2:** Effect on heart rate (beats/min.) in different group at various time intervals in atropinized dogs.

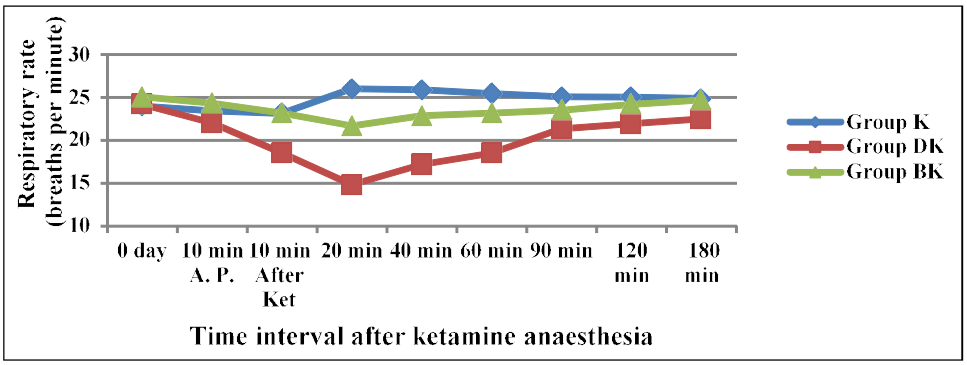


**Fig 3:** Effect on repiratory rate (breaths/min.) in different group at various time intervals in atropinized dogs.

nervous system (Kolawole, 2001). Heart rate decreased significantly ($p<0.01$) at 10 min. after premedication with dexmedetomidine in group DK. However, after induction with ketamine heart rate further decreased significantly ($p<0.05$) up to 120 min. with a peak decrease at 20 min. and values gradually increased and attained normalcy upto 180 min. of observation period as shown Fig 2. In the present study, the greater decrease in heart rate was recorded in the animals of group DK in response to premedication with dexmedetomidine alpha 2 agonist which induced bradycardia. Bradycardia occurring due to dexmedetomidine is thought to be of parasympathetic origin (Bloor *et al*., 1992). The results of the present study also conformed to the observations of Kuusela (2004) who reported decreased heart rate after dexmedetomidine administration in dogs. In group BK, a non-significant ($p<0.05$) decrease in heart rate after 10 min. of butorphanol administration was noticed which significantly ($P<0.05$) decreased at 10 min. after ketamine anaesthesia as compared to the base value and thereafter values increased towards normalcy by 180 min. of observation period. It has been reported that butorphanol facilitates the increase in parasympathetic tone and thereby contributes to bradycardia (Ko *et al.,* 2000). Similar findings were documented by Pascoe (2000) where butorphanol was given as premedicant to ketamine in dogs to record effects on heart rate. Comparison among the groups revealed no significant ($p>0.05$) difference in heart rate at any time interval.

**(c) Respiratory Rate (breaths per minute)**

The respiratory rate in group K, increased non-significantly ($p<0.05$) at 20 min. after ketamine administration which gradually decreased towards normacly by 180 min. post anaesthesia. The increase in respiratory rate in animals of group K after 20 min. of ketamine anaesthesia might be due to stimulatory action of ketamine on the respiratory centers. Wright (1982) reported that tachypnoea occurs due to a residual effect of ketamine as it activates certain subcortical areas of the CNS. The respiratory decreased non-significantly at 10 min. after premedication with dexmedetomidine in group DK. The respiratory rate continued to decrease significantly ($p<0.01$) which persisted up to 90 min. after ketamine anaesthesia with a highest decrease at 20 min. after ketamine administration as shown in Fig 3. At 120 min. respiratory rate decreased non-significantly from premedication value. After 90 min. of ketamine anaesthesia, respiratory rate gradually increased and returned to near normalcy in 180 mins. of observation. In the present study, decrease in respiratory rate might be attributed to combined effect of systemic administration of dexmedetomidine and ketamine. The depression in respiratory rate in the later stages might be due to the depressant effects of dexmedetomidine as by that time the effect of ketamine would have weaned off owing to its shorter duration. Results of the present study are in conformity with the findings of Amarpal *et al*. (1996). Demirkan *et al*. (2002) also reported significant lower respiratory rate than the baseline throughout the xylazine and ketamine anaesthesia. In group BK, there was non-significant decrease in respiratory rate at 10 min. after premedication with butorphanol. After ketamine administration, respiratory rate showed a significant ($p<0.05$) decrease in group BK between 10 to 90 min. with a peak decrease at 20 min. and values attained base level by 180 min. The decrease in respiration rate in the group BK might be due to direct depressive effect of butorphanol on medullary center in general and respiratory center in particular. The results of the present study are in agreement with the findings of Benson and Tranquilli (1992) who documented respiratory effect of butorphanol on small animal anaesthesia. Comparison among the groups revealed non-significant ($p>0.05$) difference in respiratory rate at any time interval. Therefore, the results of the present study concludes that dexmedetomidine-ketamine combination in dogs is useful anaesthetic protocol for rapid induction, prolonged duration of anaesthesia as compared to butorphanol-ketamine combination which is also useful anaesthetic protocol for short duration of anaesthesia with rapid recovery. All the physiological parameters exhibited transient changes and were maintained within normal physiological limits in all the animals during the observation period.

## CONCLUSION

Findings of the present study suggest that dexmedetomidine -ketamine provides adequate and prolonged duration of anaesthesia as compared to butorphanol-ketamine in dogs without causing any alternation in physiological parameters. Hence, dexmedetomidine-ketamine can be used safely as general anaesthesia in dogs for long duration of surgical procedures.

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