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Rajendra Singh
M.V.Sc. Scholar, Department of
Veterinary Surgery and
Radiology, College of Veterinary
and Animal Science, Navania,
Udaipur, Rajasthan, India

Evaluation of dexmedetomidine alone and in combination with butorphanol and midazolam as preanesthetic to ketamine anaesthesia in dogs

Rajendra Singh

Abstract

Objective: The main purpose of this study was to assess the efficacy of dexmedetomidine alone and in combination with butorphanol and midazolam as preanaesthetic to ketamine anaesthesia in dogs.

Animals: A total of 32 dogs divided into four groups, eight animals in each.

Methods: The dogs were premedicated with dexmedetomidine in DK, dexmedetomidine and midazolam in DMK, dexmedetomidine, butorphanol in DBK and dexmedetomidine, midazolam and butorphanol intramuscular in DBMK group. Induction and maintenance of anaesthesia were achieved with ketamine. Onset of sedation, sedation quality, induction of anaesthesia, induction dose, duration of anaesthesia, recovery quality, complete recovery time and adverse effect were recorded.

Results: Significantly longer time was required for onset of sedation in DK and DBK group then DMK and DBMK. Induction of anaesthesia in DBMK group required minimum ketamine dose. Sedation quality was moderate to severe and recovery quality was good to excellent in all dogs. Duration of anaesthesia and recovery time was slightly longer in combination groups. More than half of the dogs included in study urinated during surgical procedure or recovery time.

Conclusion and clinical relevance: It were concluded that dexmedetomidine in combination with butorphanol and midazolam serve as good pre-anaesthetics, produce quick and excellent sedation than dexmedetomidine alone.

Keywords: Dog, dexmedetomidine, general anaesthesia, opioid, sedation

Introduction

In clinical practice, anaesthesia plays important role for humane treatment and handling of the animal and provide better conditions for conducting examinations and surgical procedure (Hall, 2014) [7]. Pre-anaesthetic medication reduces fear and anxiety followed by smooth induction and recovery as well as balanced anaesthesia and ensure the safety of animal and veterinarian (Murrell, 2007) [16]. For pre-medication, available options are tranquilizer, sedative, anticholinergic and analgesic drugs. Dexmedetomidine is a new and potent α_2 - agonist. It is used as a sedative, perioperative analgesics, preanaesthetic and anaesthetic adjunct for general and regional anaesthesia (Gertler *et al.*, 2001) [6]. Butorphanol tartrate is a synthetic opioid, used to treat mild to moderate pain and induces mild sedation (KuKanich & Wiese, 2015) [11]. Synergistic interactions have been observed between α_2 - agonists and opioids and benzodiazepines (Kojima *et al.*, 2002; Salonen *et al.*, 1992) [10, 20]. Midazolam has similar pharmacological action, like other benzodiazepines, including hypnosis, sedation, anxiolysis, muscle relaxant, anticonvulsant and amnesia. It is used alone or in combination with opioids and alpha2-agonists to induce sedative and analgesic effects (Kojima *et al.*, 2002; Malik & Singh, 2008) [10, 14]. Ketamine is dissociative general anaesthetic used in combination with benzodiazepines and α_2 - agonist to subside the ketamine associated side effects like muscular hypertonicity, myoclonus and convulsions [Nesgash *et al.*, 2016] [17].

Canine practitioners commonly use xylazine-ketamine combination for minor and major surgical procedures. In veterinary practice, xylazine is oldest α_2 - agonist and associated with more profound side effects than newer available dexmedetomidine due to selectivity for α_2 - adrenoreceptor. Opioids and benzodiazepines may be added in regimen to utilise their analgesic and sedative properties as well as reducing dose rate of anaesthesia [Kojima *et al.*, 2002; Malik & Singh, 2008] [10, 14]. A need of systemic study was felt for the effects of newer α_2 - agonist and their combination with opioid and benzodiazepines. Hence the present study is planned to evaluate the effects of dexmedetomidine alone and in combination with butorphanol and midazolam to ketamine anaesthesia in dogs which markedly affect the performance.

Corresponding Author

Rajendra Singh
M.V.Sc. Scholar, Department of
Veterinary Surgery and
Radiology, College of Veterinary
and Animal Science, Navania,
Udaipur, Rajasthan, India

The present study will also help the canine practitioner for a better comprehension of anaesthetic protocols for various surgical procedures while endeavouring for a better health care of dogs.

Material and Methods

The study was conducted on 32 clients owned healthy dogs which were brought for surgery in the clinics. All the dogs included in the study were randomly divided into 4 groups viz., DK (Dexmedetomidine-ketamine), DBK (Dexmedetomidine-butorphanol-ketamine), DMK (Dexmedetomidine-midazolam-ketamine) and DBMK (Dexmedetomidine-butorphanol-midazolam-ketamine) and each group contained 8 dogs. Groupwise average age of dogs of 4 groups were between 20 to 36 month and weighed 16 to 22.7 kilogram (Table 1). Preanaesthetic evaluation of all the dogs was performed on the day before surgery. The dogs were kept off-feed and off-water for 12 and 6 hours, respectively prior to procedure. Premedication, induction and maintenance performed as mentioned in table 2. After administration of preanaesthetics, dogs were unrestrained for assessing quality of sedation (Appendix 1) and onset of sedation (Time elapsed from the beginning of pre-medication of dog till the dropping

of head or sternal recumbency) in a quiet room. Sedation score was assigned at 0, 5, 15, 20 minutes after premedication. After 20 minutes of pre-anaesthetics administration, ketamine was infused in cephalic vein to achieve induction of anaesthesia (time elapsed from beginning of administration of ketamine to dog till disappearance of pedal reflex). When pedal reflex reappeared or patient showed movement to noxious stimuli, ketamine was given I/V for maintenance of anaesthesia as per need. Dose consumed for induction of anaesthesia was noticed. After attainment of anaesthesia, surgical procedure was performed. The dogs were observed for duration of anaesthesia (time elapsed from the induction of anaesthesia to the first spontaneous movement of any body part or appearance of pedal reflex by the animal following last intermittent bolus infusion), complete recovery time (time elapsed from the appearance of pedal reflex or movement of any body parts following last intermittent bolus infusion and the ability of the dog to stand and walk without ataxia) and recovery quality (Appendix II). Statistical analysis was performed by using analysis of variance (ANOVA) with post-hoc Tukey HSD (Honestly Significant Difference) test for comparing multiple treatments.

Table 1: Mean ± Standard Error values of age and body weight in different groups

Group	Age (Month)	Body weight (Kg)
DK	20 ± 2.83 ^a	16.0 ± 2 ^a
DBK	36 ± 4.39 ^b	22.7 ± 0.95 ^b
DMK	30 ± 3.56 ^{ab}	20.5 ± 0.86 ^{ab}
DBMK	33 ± 4.42 ^{ab}	21.4 ± 0.96 ^b

Values with different superscripts differ significantly ($P < 0.05$) between the groups

DK: - Dexmedetomidine-Ketamine

DBK: - Dexmedetomidine-Butorphanol-Ketamine

DMK: - Dexmedetomidine-Midazolam-Ketamine

DBMK: - Dexmedetomidine-Butorphanol-Midazolam-Ketamine

Table 2: Premedication, induction and maintenance schedule

Group	Premedication	Induction	Maintenance
DK	Dexmedetomidine 10 mcg kg ⁻¹ bw	Ketamine intravenous until pedal reflex was lost	Intermittent bolus sized 1.2mg/kg bw as per need on movement to stimuli
DMK	Dexmedetomidine 10 mcg kg ⁻¹ bw Midazolam 0.2 mg kg ⁻¹ bw		
DBK	Dexmedetomidine 10 mcg kg ⁻¹ bw Butorphanol 0.2 mg kg ⁻¹ bw		
DMBK	Dexmedetomidine 10 mcg kg ⁻¹ bw Butorphanol 0.2 mg kg ⁻¹ bw Midazolam 0.2 mg kg ⁻¹ bw		

Ketamine: Aneket (50 mg mL⁻¹), Neon laboratories limited, Andheri (west), Mumbai, India.

Dexmedetomidine: Dextomid (100 µg mL⁻¹), Neon laboratories limited, Andheri (west), Mumbai, India

Midazolam: Mezolam (1 mg mL⁻¹), Neon laboratories limited, Andheri (west), Mumbai, India.

Butorphanol: Butodol-2 (2 mg mL⁻¹), Neon laboratories limited, Andheri (west), Mumbai, India.

Results and Discussion

In present study, injectable anaesthesia was used having dexmedetomidine, butorphanol and midazolam as preanaesthetics and ketamine for induction and maintenance

of anaesthesia and some authors (Sahoo *et al.*, 2018; Kuusela *et al.*, 2000; Sethi *et al.*, 2017) ^[19, 12, 23] advocated the doses of preanaesthetic of present study.

Table 3: Mean ± Standard Error values of anaesthetic parameters in dogs of different groups

Parameter	Groups			
	DK	DBK	DMK	DMBK
Onset of sedation (Minute)	11 ± 0.80 ^a	6.3 ± 0.46 ^b	4.1 ± 0.25 ^{cd}	2.9 ± 0.12 ^c
Onset of anaesthesia (Second)	46 ± 3.90	46 ± 2.67	55 ± 5.71	42 ± 2.71
Complete recovery (Minute)	162.5 ± 7.36	168 ± 5.67	169.5 ± 4.98	179.5 ± 5.71
Duration of anaesthesia (Minute)	11.3 ± 1.29	10.5 ± 1.19	12.7 ± 0.88	13.8 ± 1.18
Induction dose(mg)	67.5 ± 6.33	63.7 ± 5.48	61.8 ± 5.97	50.6 ± 5.62
Incremental bolus	1.25 ± 0.18	1.5 ± 0.16	1 ± 0.00	1 ± 0.00

Values with different superscripts differ significantly ($P < 0.05$) between the groups

Table 4: Mean \pm Standard Error values of the sedation score of dogs of different groups at different intervals before administration of ketamine

Group	Period of observation (minutes)			
	0	5	15	20
DK	0 \pm 0	0 \pm 0 ^a	1.25 \pm 0.16 ^{a*}	2.25 \pm 0.16 ^{a*}
DBK	0 \pm 0	0 \pm 0 ^a	2.25 \pm 0.16 ^{b*}	3 \pm 0 ^{b*}
DMK	0 \pm 0	0.62 \pm 0.18 ^{b*}	2.87 \pm 0.12 ^{c*}	3 \pm 0 ^{b*}
DBMK	0 \pm 0	1.25 \pm 0.16 ^{b*}	3 \pm 0 ^{cd*}	3 \pm 0 ^{b*}

*Bearing values significantly different from base value ($P < 0.05$)

Values with different superscripts differ significantly ($P < 0.05$) between the groups

In DK group, time 11 ± 0.80 minutes for sedation was significantly higher than DBK, DMK and DBMK. After I/M administration, dexmedetomidine have delayed onset of sedation (Bennett & Restitutti, 2016) [3]. In previous studies, Micieli *et al.* (2017) recorded time of onset of sedation 9.4 ± 4.6 minutes with dexmedetomidine $20 \mu\text{g kg}^{-1}$ I/M. Time for the onset of sedation in DBK group was significantly higher than the DMK and DBMK groups. Combinations of benzodiazepine and opioid with α_2 - agonists induced profound sedation due to synergism with α_2 - agonist (Kojima *et al.*, 2002; Salonen *et al.*, 1992) [10, 20]. In this study, the different combination of dexmedetomidine with butorphanol and midazolam resulted in a decrease in the onset of sedation time 6.3 ± 0.46 minutes in DBK, 4.1 ± 0.25 in DMK and 2.9 ± 0.12 in group DBMK. Similarly, Santosh *et al.* (2013) [21] and Sahoo *et al.* (2018) [19] reported onset of sedation within 5 - 25 minutes (range) after dexmedetomidine $5 \mu\text{g kg}^{-1}$ and butorphanol 0.3 mg kg^{-1} , 4.3 ± 0.23 minutes after dexmedetomidine $10 \mu\text{g kg}^{-1}$ and midazolam 0.4 mg kg^{-1} I/M and 3 ± 0.89 and 2.5 ± 0.22 minutes after dexmedetomidine $10 \mu\text{g kg}^{-1}$ butorphanol 0.2 mg kg^{-1} midazolam 0.2 mg I/M , respectively.

All dogs were observed for 20 minutes after premedication in a calm and quiet environment for sedative effect. This period may have allowed each drug to act optimally, thereafter sedation level of dogs considered ideal for induction of anaesthesia. All dogs in DK group exhibited moderate-severe sedation at 20 minutes after premedication (Ahmad *et al.*, 2013) [1] and severe sedation was observed in groups DBK, DMK and DBMK where dexmedetomidine used in different combination with butorphanol and midazolam. In a previous study, Selmi *et al.* (2003) [22] reported deeper sedation with dexmedetomidine-opioids combination. Combination groups scored significantly high sedation score at 5, 15, 20 minutes (Table 4 post premedication than dexmedetomidine alone may be due to the synergistic interaction between sedative properties of butorphanol and midazolam (Kojima *et al.*, 2002; Salonen *et al.*, 1992) [10, 20]. Contrary, LeChevallier *et al.* (2018) noticed moderate sedation and paradoxical behaviour in healthy dogs after intravenous administration of combinations of medetomidine and midazolam.

The values of induction of anaesthesia were non-significant between the groups. Dogs of DBMK group required less time (42 ± 2.71 seconds) for induction of anaesthesia while DK and DBK took same time (46 ± 3.90 and 46 ± 2.67 seconds). However, Bisht (2017) [4] observed induction within 60 ± 8.76 and 55 ± 5.70 seconds in dexmedetomidine $10 \mu\text{g kg}^{-1}$ I/V premedicated dog. Arunkumar *et al.* (2017) [2] noticed quicker induction within 57 ± 0.99 seconds with propofol after I/V administration of dexmedetomidine $10 \mu\text{g kg}^{-1}$. Whereas, Sahoo *et al.* (2018) [19] noticed the induction of anaesthesia within 1.5 ± 0.22 minutes using ketamine after atropine-meloxicam-dexmedetomidine-midazolam-butorphanol premedication.

In the present study, the total dose of ketamine consumed for induction of anaesthesia was greater in DK ($67.5 \pm 6.33 \text{ mg}$) and minimum ($50.6 \pm 5.62 \text{ mg}$) for DBMK group. The values of induction dose were non - significant between the groups. The anaesthetic sparing effect of α_2 - adrenoceptor drugs are directly proportional to their specificity to α receptor (Salonen *et al.*, 1992) [20].

Some authors (Sahoo *et al.*, 2018; Jena *et al.*, 2014) [19, 8] also noticed a reduced anaesthetic dose requirement for induction after premedication with dexmedetomidine, butorphanol and midazolam in different regime as noticed in present study. Kojima *et al.* (2002) [10] observed reduced anaesthetic induction dose in cats after medetomidine-midazolam premedication in comparison to midazolam-butorphanol and acepromazine-butorphanol. Contrary, Santosh *et al.* (2013) [21] noticed high induction dose of ketamine, when dexmedetomidine was used $10 \mu\text{g kg}^{-1}$ and $20 \mu\text{g kg}^{-1}$, were $9.04 \pm 0.59 \text{ mg kg}^{-1}$ and $8.93 \pm 0.83 \text{ mg kg}^{-1}$, respectively.

In present study duration of anaesthesia was 24.5 ± 1.23 , 25.2 ± 0.75 , 26.1 ± 1.43 and 27.6 ± 1.06 minutes in group DK, DBK, DMK and DBMK, respectively. It was comparatively longer in combination groups. Fluctuation in the duration of anaesthesia between groups was non-significant. Authors (Sahoo *et al.*, 2018; Selmi *et al.*, 2003) [19, 22] corroborated with the findings of duration of anaesthesia in present study. Preanaesthetic protocols having midazolam as a part of regime in the present study, used less incremental bolus of ketamine for maintenance of anaesthesia and longer duration of anaesthesia may be due to the hypnotic property of midazolam (Nordt and Clark, 1997) [18].

Slightly longer complete recovery time in DBMK (179.5 ± 5.71 minutes) followed by DMK (169.5 ± 4.98 minutes), DBK (168 ± 5.67 minutes) in combination groups resulted from the synergistic action between dexmedetomidine, butorphanol, midazolam, and ketamine resulting in deeper sedation and reduced metabolic activity delay redistribution and metabolism of the drugs (Ko *et al.*, 2000) [9]. Mean \pm SD value of complete recovery time in all groups were between 160-180 minutes. Similarly, Authors (Santosh *et al.*, 2013, Ahmad *et al.*, 2013) [21, 1] also advocated complete recovery time of present study.

Good to excellent quality of recovery was observed in dogs of all groups while excellent, smooth and uneventful recovery were observed after premedication by Jena *et al.* (2014) [8] with dexmedetomidine alone and Sahoo *et al.* (2018) [19] with combination of dexmedetomidine $10 \mu\text{g kg}^{-1}$, butorphanol 0.2 mg kg^{-1} and midazolam 0.2 mg kg^{-1} I/M. In present study, recovery time was longer due to slow biotransformation of dexmedetomidine with elimination half-life was 47 minutes slow (Sethi *et al.*, 2017) [23].

More than half (17) number of the dogs included in the study were urinated copiously during the recovery. Jena *et al.* (2014) [8] also observed urination in both xylazine and dexmedetomidine premedicated dogs. It may be due to central

stimulation of α_2 - adrenoceptor in the hypothalamus and osmotic diuretic effect of increased blood glucose by α_2 – agonists. Nausea was observed in two dogs (DK and DMK group) in present study which may be due to stimulation of receptors in the CTZ in the brain by the α_2 - adrenoceptor agonist (Botero *et al.*, 2011) [5]. However, Selmi *et al.* (2003) [22] did not observe nausea/vomiting in cats after administration of dexmedetomidine, butorphanol and ketamine in different combination.

In healthy dogs, dexmedetomidine was observed as good pre-anaesthetic in combination with butorphanol and midazolam for the quicker onset of sedation, excellent quality of sedation, an anaesthetic sparing effect and consumed less ketamine for onset of anaesthesia with shorter time and ensured a longer duration of anaesthesia. Dexmedetomidine alone may be better option for sedation to avoid prolonged recovery.

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Conflict of interest

Author declare no conflict of interest.

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Appendix 1: Sedation quality and scoring description

Score	Category	Description
0	No sedation	No signs of depression, drowsiness or ataxia and fully alert
1	Mild	Mild signs of depression, drowsiness or ataxia. Decreased reaction to stimuli
2	Moderate	Severe ataxia, reluctant to move, may attain sternal recumbency
3	Severe	Depressed, drowsy and sleepy, no resistance to positioning on lateral recumbency

Appendix 2: Recovery quality description

Type of recovery	Description
Excellent	No paddling, tremors or other unconscious moment. No vocalization, salivation normal, not excessive. Transferred from lateral recumbency to sternal recumbency with one or two attempts.
Good	No vocalization and paddling, salivation may be increased. More than two attempts may be required to transition from lateral to sternal recumbency.
Fair	Moderate paddling, Hyper salivation and Vocalization present. The patient showed difficulty in positioning itself, may thrashed about for short period and manual restraint may be required for short periods.
Poor	Regular unconscious movements persisted well into consciousness, thrashing for a sustained period and animal injured itself without manual restraint. May responded aggressively to restraint. Hyper salivation and sustained vocalization.