Indian J. Vet. Surg. 45(1): 21-26 June 2024

ijvs

Multimodal balanced general anaesthesia using tiletamine-zolazepam, butorphanol, dexmedetomidine, propofol, ketamine and lignocaine in dogs

Sruthi Chandramohan[1], S. Sooryadas[2†], P.T. Dinesh[2], N.S. Jineshkumar[2], V. Remya[2], S. Anoop[3] and P. Vinu David[4]

Kerala Veterinary and Animal Sciences University, Pookode, Wayanad- 670 643 (Kerala)

[1]MVSc Scholar, [2]Assistant Professor, [3]Professor and Head, Department of Veterinary Surgery and Radiology, [4]Associate Professor, Department of Veterinary Clinical Medicine, Ethics and Jurisprudence, College of Veterinary and Animal Sciences, Pookode

DOI: 10.5958/0973-9726.2024.00004.4 *Received: .April 2023*

Ten adult dogs of different ages, belonging to either sex and categorized as ASA class I, II or III, posted for various surgeries were premedicated with meloxicam (0.2 mg/kg body wt) and sedated using a combination of dexmedetomidine (5 mcg/kg), butorphanol (0.2 mg/kg), tiletamine-zolazepam (2mg/kg) administered intramuscularly. Anaesthesia was induced with propofol administered intravenously 'to effect'. Upon anaesthetic induction, all the animals were intubated and provided 100% oxygen through a suitable breathing circuit from an anaesthesia machine. Following induction of anaesthesia and endotracheal intubation, all animals were administered a loading dose of lignocaine (2 mg/kg body wt) intravenously. Anaesthesia was then maintained using two CRIs – one comprising a combination of dexmedetomidine (2 mcg/kg/hr), lignocaine (50 µg/kg/min) and ketamine (40 µg/kg/min), and the other propofol (50 µg/kg/min), administered simultaneously through a three-way stopcock connected to the intravenous cannula.

The results indicated that the combination of tiletamine-zolazepam, butorphanol and dexmedetomidine provided profound sedation. Induction of anaesthesia could be achieved with propofol @ 0.58±0.06 mg/kg body wt, intravenously. Anaesthesia could be maintained with constant rate infusions of dexmedetomidine, lignocaine and ketamine, or with propofol following a loading dose of lignocaine, without compromising cardiovascular functions. The protocol provided excellent analgesia for various soft tissue and orthopaedic procedures. Some of the complications like respiratory depression resulting in hypoventilation could easily be managed by assisted ventilation. Nociception noticed with some severely painful orthopaedic manoeuvres could also be managed by supplementing ketamine at its analgesic doses.

***Key words**: Balanced anaesthesia, Butorphanol, Dexmedetomidine, Dog, Isoflurane, Multimodal general anaesthesia, Tiletamine, Zolazepam*

Multimodal balanced anaesthesia works on the principle that smaller quantities of various nervous system depressants add to the advantages but not the disadvantages of the individual drugs used. This principle helps in maximising the desired effects and minimising the undesired effects of each drug since all the drugs are used at lower doses. The drugs chosen act synergistically to bring about the anaesthetic triad, namely unconsciousness, muscle relaxation and analgesia. Analgesics from two or more classes or analgesic techniques that utilize different mechanisms of action are combined to target different nociceptive pathways. The current study was conducted with the aim of evaluating the effects of a combination of tiletamine-zolazepam, butorphanol and dexmedetomidine for sedation, and anaesthesia using propofol, ketamine, dexmedetomidine and lignocaine in dogs undergoing various surgeries.

Materials and Methods

The constant rate infusion (CRI) of dexmedetomidine, lignocaine and ketamine was prepared as a single solution (DLK) in an infusion bottle, while propofol was prepared as a separate solution in a syringe. The DLK and propofol CRIs were prepared separately for the reason that, propofol and lignocaine are not compatible to be mixed in a single solution. Both these CRIs were administered to all the studied animals simultaneously, using two devices – a volumetric infusion pump for the DLK and a syringe pump for the propofol. A three-way stopcock was connected to each patient's intravenous cannula to facilitate the administration of the above two CRI solutions.

The CRI of dexmedetomidine, lignocaine and ketamine was prepared as per the steps mentioned below:

a) Calculated total milligrams (or micrograms) of drug needed per hour
   i) For lignocaine and ketamine -
   Amount of drug (mg) = CRI dose of drug (mcg/kg/min) x body weight (kg) x 60 (min)

   1000 (mcg)
   ii) For dexmedetomidine
   Amount of drug (mcg) = CRI dose of drug (mcg/kg/hr) x body weight (kg)
b) Calculated the volume of fluid (CRI infusion solution) to be delivered per hour, i.e. mL/hr =

†Corresponding author; E-mail: sooryadas@kvasu.ac.in

rate of flow of CRI (mL/kg/hr) x body weight (kg)
(The rate of flow of CRI was chosen as 10 mL/kg/hr as per intra operative fluid requirement)

Figured out how many milligrams (of lignocaine and ketamine) or micrograms (of dexmedetomidine) is needed per mL of the infusion

$$= \frac{\text{mg (or mcg) of drug per hour}}{\text{mL of infusion per hour}}$$

Decided the total mL of the infusion planned to be delivered.

The milligrams or micrograms of the drug per mL of infusion obtained in the above step was multiplied by 100 or 500 in case of 100 mL or 500 mL NS bottles, respectively, to get the amount of drug (in mg) required to be added. The total milligram or microgram of the drug to be added was divided by the presentation of the respective drugs to obtain the volume of each drug required for preparation of CRI. These volumes were totaled, and an equal amount of fluid from the 100 or 500 mL bottle was drawn and discarded. The volumes of dexmedetomidine, lignocaine and ketamine were added to the infusion fluid to make up 100 mL or 500 mL of the CRI. This was then administered at 10 mL/kg/hr using the volumetric infusion pump so as to deliver dexmedetomidine @ 2 mcg/kg/hr, lignocaine @ 50 mcg/kg/min and ketamine @ 40 mcg/kg/min.

The CRI of propofol was prepared by calculating the amount of propofol (in mg) as per the formula mentioned. The result obtained was divided by presentation of the drug to obtain the volume of propofol required for infusion. Double the volume of propofol was taken in a 20 mL syringe and extended to 20 mL with normal saline. This calculated and extended propofol solution was administered at 10 mL/hr to last for 2 hr, delivering propofol at a CRI dose of 50 mcg/kg/min. This was done to minimize the breaks associated with changing syringes in the volumetric syringe pump.

Ten adult dogs undergoing various soft tissue and orthopaedic surgeries were included in the study, details of which are presented in table 1. All dogs were administered with meloxicam (0.2 mg/kg body wt, i.m.), as pre-emptive analgesic, and were then prepared for the surgeries. 30 min after administration of meloxicam, all dogs were administered a combination of tiletamine-zolazepam (2 mg/kg body wt), butorphanol (0.2 mg/kg) and dexmedetomidine (5 mcg/kg), which were taken in a single sterile syringe and given intramuscularly.

Upon sedation, anaesthesia was induced in all dogs with propofol loaded (1 mg/kg body wt) in a 10 mL syringe and extended to 10 mL using normal saline administered intravenously 'to effect' permitting endotracheal intubation. All the animals were then connected to a suitable breathing circuit from the anaesthesia machine to provide 100% oxygen. Following induction of anaesthesia with propofol, a loading dose of lignocaine (2 mg/kg body wt) was administered intravenously, and the CRIs of dexmedetomidine, lignocaine and ketamine (DLK) and that of propofol were initiated simultaneously through the three-way stop-cock.

The dogs which exhibited somatic or visceral nociception intra-operatively were administered micro-dose(s) of ketamine or dexmedetomidine intravenously, as the case warranted. The doses of the drugs thus administered were recorded.

The quality of anaesthetic induction, maintenance and recovery was noted, along with degree of anaesthesia, analgesia and muscle relaxation. Time for sedation, time for recovery, abolition and regaining of reflexes were monitored along with physiological and biochemical parameters and complications during anaesthesia. Subjective analysis of the degree of anaesthesia achieved was done based on the presence or absence of reflexes including palpebral reflex, pedal reflex, skeletal muscle

Table 1: Signalment of the animals used and their surgical conditions.

Dog ID	Breed	Age	Sex	Body weight	ASA class	Temperament	Surgical condition/ procedure presented
D1	Spitz	6 yr	Male	9.6 kg	III	Calm	Femur fracture - plating
D2	Rottweiler	7 m	Female	27.3 kg	I	Aggressive	Tibial tuberosity avulsion–tension band wiring
D3	Non-descript	9.5 m	Female	15.8 kg	I	Anxious	Ovariohysterectomy
D4	Non-descript	3 yr	Female	16.5 kg	I	Anxious	Ovariohysterectomy
D5	Labrador Retriever	3 yr	Female	30 kg	III	Bright, alert, responsive	Vaginal hyperplasia-excision
D6	Non-descript	5.5 yr	Female	14.7 kg	I	Calm	Ovariohysterectomy
D7	Doberman	9 m	Female	23.4 kg	I	Calm	Supracondylar fracture of femur–cross pinning
D8	Spitz	1.5 yr	Female	5 kg	II	Anxious	Radius ulna fracture-plating
D9	Non-descript	1 yr	Female	13.4 kg	I	Calm	Ovariohysterectomy
D10	Labrador Retriever	7 m	Female	22 kg	I	Active	Supracondylar fracture of femur-cross pinning

relaxation and position of eyeball. Time taken for sedation was noted as the time (in min) taken from intramuscular administration of tiletamine-zolazepam-butorphanol-dexmedeto-midine to attainment of lateral recumbency with loss of righting reflex and abolition of jaw muscle tone. The dose of propofol (mg/kg) which was administered intravenously 'to effect' for induction of anaesthesia to facilitate endotracheal intubation was noted.

Quality of induction was judged based on the degree of sedation and smoothness of anaesthetic induction. Quality of maintenance was judged based on analgesia achieved, degree of muscle relaxation, absence of response to surgical stimuli and maintenance of physiological parameters. The time taken for recovery was noted as the time period in minutes from stoppage of CRI to the rejection of endotracheal tube. The quality of recovery was judged based on the character of transition from anaesthesia to consciousness.

Physiological parameters such as rectal temperature (°C), heart rate and pulse rate (beats/min), rate of respiration (breaths/min), haemoglobin oxygen saturation SpO_2 (%), end tidal carbon dioxide (ETCO2), non-invasive blood pressure (NIBP), electrocardiogram (ECG), blood gases and electrolytes, and serum biochemical parameters were recorded.

The data obtained during the study were subjected to statistical analysis using the statistical software SPSS version 24.0.

Results and Discussion

The observations on signs associated with sedation and time taken for sedation are presented in table 2. Savas *et al.* (2001) also had similar observation of paddling of limbs, salivation, head rocking and tongue curling in a dog anaesthetised with tiletamine-zolazepam administered @ 10 mg/kg intramuscularly. The mean time taken for sedation was 6.18±1.34 min. Barletta *et al.* (2011) also observed that the time of onset of sedation ranged from 1.6 min to 3.6 min when sedated with intramuscular administration of dexmedetomidine-ketamine-opioid combination, and that all animals attained peak sedation within 4-6 min of injection. Profound sedation was achieved in all the dogs studied, similar to observations by Krimins *et al.* (2012). Induction of anaesthesia with propofol was smooth and intubation was easy in all the animals of the current study. Cullen and Reynoldson (1997) also reported smooth induction of anaesthesia with intravenous administration of propofol after premedication with tiletamine-zolazepam.

The dose of propofol which was required for induction of anaesthesia ranged from 0.3 to 0.8 mg/kg with a mean of 0.58±0.06 mg/kg. Considerably lower doses of propofol required for anaesthetic induction could be attributed to the synergistic effects of premedicants used in the sedation protocol.

The relaxation of muscles of limbs, abdomen and jaw were graded as excellent in all 10 animals studied. Pedal and palpebral reflexes abolished, and eyeballs rotated ventromedially following peak sedation and remained in the same state till recovery. The quality of anaesthesia was judged as good to excellent.

No signs of nociception were observed at any time during the surgery, except at times where severely painful stimuli were induced. Transient nociception was observed in 4 dogs, out of which two dogs were given analgesic doses of ketamine (0.5 mg/kg body wt). These two dogs were undergoing orthopaedic procedures in which nociception persisted following the use of periosteal elevator on bone. From these findings it could be assumed that the studied combination provided excellent and profound surgical plane of anaesthesia and excellent analgesia

Table 2: Signs associated with sedation and time taken for onset of sedation.

Dog ID	Signs preceding sedation and their respective time from administration of the anaesthetic combination					
	Salivation (min)	Ptosis (min)	Head movements (min)	Head down (min)	Sternal recumbency (min)	Time taken for sedation (min)
D1	Not exhibited	2.75	2.0	3.0	3.0	3.36
D2	Not exhibited	3.9	Not exhibited	4.41	4.41	5.41
D3	Not exhibited	3.0	Not exhibited	12.1	13.41	14.68
D4	3.25	4.41	4.0	5.2	7.91	12.33
D5	Not exhibited	2.5	Not exhibited	2.0	2.0	3.0
D6	Not exhibited	5.41	4.16	6.13	4.5	7.41
D7	Not exhibited	4.5	3.96	5.0	5.25	6.25
D8	4.0 (intense)	1.71	2.33	2.58	2.46	4.5
D9	Not exhibited	1.88	1.71	1.83	1.38	1.83
D10	3.26	2.13	Not exhibited	2.28	2.0	3.0
Mean±SE (in min)		**3.20±0.40**		**4.46±0.98**	**4.63±1.15**	**6.18±1.34**

for procedures on soft tissues, and moderate to profound analgesia for procedures on bone. Nociception which needs to be managed may be expected only during severely painful steps in the surgical procedures.

Signs associated with recovery were return of eyeballs to central position, return of palpebral reflex, return of pedal reflex, return of jaw muscle tone, rejection of endotracheal tube, head lift, sternal recumbency and standing unassisted. All the observations on recovery parameters are presented in table 3.

Fall in core body temperature towards latter half of anaesthetic maintenance was observed in all 10 animals, and were hypothermic postoperatively. Body temperature was managed with the help of patient warmer and by administering warm fluids intravenously. The decrease in body temperature could be attributed to peripheral vasodilation, decrease of basal metabolic rate and depression of thermoregulatory mechanism in the intra-operative period (Koc *et al.*, 2002).

There was a significant reduction in heart rate and pulse rate from baseline values in all the animals studied. But mean arterial blood pressure was towards higher limits of normal values, and some dogs were hypertensive at different time points. On ECG, sinus arrhythmia was observed in 3/10 dogs studied, and rest of the dogs showed sinus rhythm. The physiological increase in blood pressure and reflex bradycardia, with concurrent increase in cardiac output, could be due to the effect of peripheral vasoconstriction caused by dexmedetomidine (Murrell and Hellebrekers, 2005).

Rate of respiration reduced following induction of anaesthesia in all the dogs studied. Two dogs, following induction, had transient apnoea. The end tidal carbon dioxide concentrations ($ETCO_2$) following induction of anaesthesia was observed to be higher than normal limit in all animals. The character of respiration following anaesthetic induction and during the period of surgery was not ideal to maintain eucapnea in any of the animals. Ventilation was hence assisted in all the animals by squeezing the reservoir bag to peak inspiratory pressures ranging from 15 to 20 cm H_2O at rates varying from 4 to 15 breaths/ min so as to maintain eucapnea. The increase in $ETCO_2$ following induction indicated depression of ventilation functions as a result of depression of respiratory centres by the anaesthetic combination. According to Ko (2013), hypoventilation occurs as a result of CNS depression at the respiratory centre caused by the anaesthetic drugs, and can be easily managed by assisting ventilation by sighing/ squeezing the reservoir bag or with the help of mechanical ventilators.

Values of peripheral oxygen saturation of haemoglobin following anaesthetic induction and during maintenance of anaesthesia was above 90% in 8 animals. Even though all the animals were administered 100% oxygen, SpO_2 values were found low in two animals. The lower values of SpO_2 could be attributed to the effect of dexmedetomidine used in the study. DeMeulenaere (2007) has suggested that pulse oximetry may not give correct readings when there is peripheral vasoconstriction.

The P_vCO_2 values after recovery from anaesthesia was significantly higher, and pH values of venous blood after recovery was significantly lower in all the animals when compared to the baseline values, indicating respiratory acidosis (Bachmann *et al.*, 2018). This could be attributed to the reduced clearance of

Table 3: Recovery parameters in different dogs.

Dog ID	Signs associated with recovery and their respective times (min) following weaning from CRI					Time taken for recovery (min)	Quality of recovery
	Return of eyeballs to centre (min)	Return of pedal reflex (min)	Head lift (min)	Sternal recumbency (min)	Standing unassisted (min)		
D1	51	31	64	121	*	55	Smooth
D2	24	33	37	53	*	27	Smooth
D3	43	35	48	52	120	54	Smooth
D4	25	28	30	31	60	30	Smooth
D5	70	84	109	114	199	74	Transient delirium
D6	13	10	15	15	42	14	Smooth
D7	30	26	37	42	*	32	Smooth
D8	44	40	49	49	85	45	Smooth
D9	29	29	40	44	95	30	Smooth
D10	22	20	26	26	*	24	Smooth
Mean ±SE	**35.1±5.33**	**33.6±6.18**	**45.5±8.25**	**54.7±11.15**	**100.17±22.67**	**38.5±5.72**	

*Recording the time taken for 'standing unassisted' was avoided in these animals since they underwent hind limb surgeries.

carbon dioxide from the alveoli following rejection of endotracheal tube. The oxygen tension (P_vO_2), bicarbonate and base excess values showed no significant changes in any of the dogs between the pre-induction, post-induction and post-recovery values.

The blood lactate values after recovery from anaesthesia were significantly lower in all the animals when compared to their baseline values. Blood lactate levels are known to indicate the adequacy of tissue perfusion, with increased lactate levels indicating hypoperfusion (Uilenreef *et al.*, 2008). Lactate levels may have decreased in the current study due to increased tissue perfusion associated with the protocol.

The serum alanine amino transferase values after recovery was significantly lower in all the animals when compared to the baseline values, as also reported by Manasa *et al.* (2021). The creatinine values after recovery was significantly lower in all the animals when compared to the baseline values. Creatinine values are known to increase in anaesthetic period due to decreased renal blood flow and glomerular filtration rate induced by the action of anaesthetic drugs (Saikia *et al.*, 2022). In the present study, decreased levels of creatinine after recovery might indicate adequate perfusion of kidneys during anaesthesia. The blood glucose values after recovery were significantly higher in all the animals when compared to the baseline values. Increase in blood glucose level has been observed with the use of á2 adrenergic agonists (Restitutti *et al.*, 2012; Ansari *et al.*, 2019). Total protein, albumin and globulin and BUN levels showed no significant changes.

The potassium values after recovery was significantly higher in all the animals when compared to the baseline values. This result was contrary to observations by Ratnesh *et al.* (2014) who have recorded decreased serum potassium levels. The chloride levels after recovery were significantly higher in all the animals when compared to the baseline values. The increase in chloride values could be attributed to fluid therapy and CRI using normal saline (Khanna, 1997; Uilenreef *et al.*, 2008). The sodium and calcium values showed no significant changes between the pre-induction, post-induction and post-recovery values.

From the results of this study, it could be concluded that the combination of tiletamine-zolazepam (2 mg/kg), butorphanol (0.2 mg/kg) and dexmedetomidine (5 mcg/kg) provided profound sedation when administered intramuscularly. Smooth induction of anaesthesia could be achieved with tiny dose of propofol (0.58±0.06 mg/kg) administered intravenously. Anaesthesia could be maintained by constant rate infusions of dexmedetomidine (2 mcg/kg/hr), lignocaine (50 mcg/kg/min), ketamine (40 mcg/kg/min) and propofol (50 mcg/kg/min) following a loading dose of lignocaine (2 mg/kg), without compromising cardiovascular functions. The protocol provided excellent analgesia for various soft tissue and orthopaedic procedures. The transient respiratory depression resulting in hypoventilation could easily be managed by assisting ventilation manually or mechanically. Nociception noticed with some severely painful orthopaedic manoeuvres could be easily managed by supplementing ketamine at its analgesic doses.

Acknowledgements

The authors acknowledge the support and facilities provided the Dean, College of Veterinary and Animal Sciences, Pookode, Wayanad, Kerala for the current study.

References

Ansari, H., Purohit, S., Chaurasia, M.K. and Pandey, R.P. 2019. Evaluation of midazolam ketamine-xylazine and propofol-ketamine combinations for maintenance of anaesthesia by constant rate infusion (CRI) in canine: haemato-biochemical study. Indian J. Vet. Surg. **40**: 58-61.

Bachmann, K., Kutter, A.P., Jud Schefer, R., and Sigrist, N.E. 2018. Determination of reference intervals and comparison of venous blood gas parameters using a standard and nonstandard collection method in 51 dogs. Schweizer Archivfür Tierheilkunde **160**: 163-170.

Barletta, M., Austin, B.R., Ko, J.C., Payton, M.E., Weil, A.B. and Inoue, T. 2011. Evaluation of dexmedetomidine and ketamine in combination with opioids as injectable anaesthesia for castration in dogs. J. Am. Vet. Med. Assoc. **238**: 1159–1167.

Cullen, L.K. and Reynoldson, J.A. 1997. Effects of tiletamine/zolazepam premedication on propofol anaesthesia in dogs. Vet. Rec. **140**: 363–366.

DeMeulenaere, S. 2007. Pulse oximetry: uses and limitations. J. Nurse Pract. **3:** 312-317.

Khanna, C. 1997. Fatal hypernatremia in dogs from salt indigestion. J. Am. Anim. Hosp. Assoc. **33**: 1-13.

Ko, J.C. 2013. Small Animal Anaesthesia and Pain Management in Dogs and Cats. 1st edn. Manson Publishing Ltd. P 336.

Koc, Y., Alkan, F. and Kul, M. 2002. Effects of anaesthetic like combination of midazolam and xylazine on certain clinical parameters in dogs. Indian Vet. J. **79**: 1281-1284.

Krimins, R.A., Ko, J.C., Weil, A.B. and Payton, M.E. 2012. Evaluation of anaesthetic, analgesic, and cardiorespiratory effects in dogs after intramuscular administration of dexmedetomidine–butorphanol-tiletamine-zolazepam or dexmedetomidine-tramadol-ketamine drug combinations. Am. J. Vet. Res. **73**: 1707-1714.

Manasa, M.R., Dileepkumar, K.M., Anoop, S., Ramankutty, S., Beena, V. and John Martin, K.D. 2021. Evaluation of haematological and serum

biochemical profile of propofol induced isoflurane anaesthesia in geriatric dogs premedicated with diazepam and butorphanol. J. Vet. Anim. Sci. **52**: 81-84.

Murrell, J.C. and Hellebrekers, L.J. 2005. Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet. Anaesth. Analg. **32**: 117–127.

Ratnesh, Peshin P.K., Kumar, A. and Singh, S. 2014. Effects of propofol on haematological and blood biochemical profile of buffalo calves. Indian J. Vet. Surg. **35**: 25-27.

Restitutti, F., Raekallio, M., Vainionpää, M., Kuusela, E. and Vainio, O. 2012. Plasma glucose, insulin, free fatty acids, lactate and cortisol concentrations in dexmedetomidine sedated dogs with or without MK-467: a peripheral á-2 adrenoceptor antagonist. Vet. J. **193**: 481-485.

Saikia, B., Sarma, K.K. and Sarma, K. 2022. Effects of propofol, ketamine and their combination (ketofol) as total intravenous anaesthesia (TIVA) on haematological, serum biochemical and hormonal profile in the surgical management of canine patients. Indian J. Anim. Res. **56**: 866-872.

Savas, I., Plevraki, K. and Raptopoulos, D. 2001. Aerophagia and gastric dilation following tiletamine/zolazepam anaesthesia in a dog. Vet. Rec. **149**: 20–21.

Uilenreef, J.J., Murrell, J.C., McKusick, B.C. and Hellebrekers, L.J. 2008. Dexmedetomidine continuous rate infusion during isoflurane anaesthesia in canine surgical patients. Vet. Anaesth. Analg. **35**: 1-12.