RESEARCH ARTICLE

Comparative Evaluation of Ketamine-Diazepam and Tiletamine-Zolazepam Induction Anaesthesia with Isoflurane Maintenance in Dogs

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Abstract

The present anaesthetic study was conducted in twelve dogs requiring general anaesthesia for surgical procedures, which were randomly divided into two groups. Induction of anaesthesia was achieved by intravenous administration of tiletamine @ 2.5 mg/kg b.wt. with zolazepam @ 2.5 mg/kg b.wt. in group I, and ketamine @ 5 mg/kg b.wt. with diazepam @ 0.5 mg/kg b.wt. in group II and then maintained by isoflurane in both groups. Anaesthetic, clinico-physiological and haemato-biochemical parameters were evaluated at different time intervals. The tiletamine-zolazepam combination showed better induction quality than the ketamine-diazepam combination, although both combinations had fair to excellent quality. Excellent maintenance quality anaesthesia with smooth and rapid recovery was observed with isoflurane. Non-significant differences were found in haemato-biochemical parameters between the groups and between time periods post-induction. However, significant differences were recorded in clinico-physiological parameters within the groups at different time periods.Few complications were encountered during induction and maintenance in both groups.

Key words: Diazepam, Dog, Isoflurane, Ketamine, Tiletamine, Zolazepam.

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Introduction

General anaesthesia is a state of reversible unconsciousness produced by drug-induced depression of the central nervous system (CNS) characterized by amnesia, analgesia, muscular relaxation and suppression of reflexes to noxious surgical stimuli (Tonner, 2005). In canine patients, this can be achieved by either total intravenous anaesthesia (TIVA) or inhalation anaesthesia (Thurmon and Short, 2007). TIVA is a simple and easy procedure requiring no sophisticated instruments, but it is associated with prolonged recovery and recumbency time; while inhalation anaesthesia is safe for longer procedures as it provides proper control on the depth of anaesthesia, facilitates rapid recovery and is less toxic to the patients. The disadvantages of TIVA can be compensated for by induction with an intravenous agent followed by maintenance with an inhalant anaesthetic agent.

Ketamine and tiletamine produce dissociation of the limbic and thalamocortical systems, which is described as a state of "dissociative anaesthesia". They have a rapid onset and provide somatic analgesia (De Caro Carella, 2016). Diazepam and zolazepam are benzodiazepine pre-anaesthetic drugs with sedative, anxiolytic, muscle relaxant and anticonvulsant properties. Dissociative anaesthetic agents are used in conjunction with benzodiazepines to ameliorate the central excitatory effects they cause, which improves the quality of induction (Clarke and Trim, 2013). Isoflurane is the most commonly used inhalant anaesthetic agent to maintain general anaesthesia in dogs (Steffey *et al.,* 2015). It has several advantageous properties such as low blood solubility, low biodegradability, short induction and recovery time (Kenna and Jones, 1995). The present study was undertaken to evaluate and compare the clinico-physiological and haemato-biochemical effects of combination of ketamine-diazepam and tiletamine-zolazepam as an induction agents and isoflurane for maintenance in canine patients undergoing surgical procedures.

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Materials And Methods

Twelve clinical cases of dogs (n=12) presented to Department of Veterinary Surgery and Radiology, College of Veterinary Science, Navsari (Gujarat, India) undergoing surgical interventions were randomly assigned into two groups of six

animals each irrespective of age, breed, sex, body weight and surgical procedure. Induction of anaesthesia was achieved by intravenous administration of tiletamine @ 2.5 mg/kg b.wt. with zolazepam @ 2.5 mg/kg b.wt. in group I (n=6), and ketamine @ 5 mg/kg b.wt. with diazepam @ 0.5 mg/kg b.wt. in group II(n=6). Endotracheal intubation was carried out with a suitable endotracheal tube under the guidance of laryngoscope in sternal or lateral recumbency by spraying lignocaine 2% spray at the larynx. The endotracheal tube was connected with the breathing circuit (Bain co-axial) of small animal inhalant anaesthetic machine. Flow rate of 100% oxygen was set as per the animal's tidal volume and anaesthesia was maintained by isoflurane in all the animals. The vaporizer setting was adjusted according to the depth of anaesthesia required while monitoring the animal's response.

Evaluation of anaesthetic protocols was done based on the observations of duration of maintenance of anaesthesia, duration of surgery,total duration of anaesthesia and recovery time. The quality of induction anaesthesia was assessed by scoring system graded on score scale of 1 to 4 as suggested by Singh *et al*. (2012) and Dinesh *et al*. (2019). The quality of maintenance anaesthesia was assessed based on a scoring scale including parameters like pedal reflex, palpebral reflex, jaw tone and eyeball position as reported by Singh *et al*. (2012).

The clinico-physiological parameters, *viz*., rectal temperature (°F), pulse rate (beats/min), respiration rate (breaths/min), systolic, diastolic and mean arterial blood pressure (mm Hg) and saturation of peripheral oxygen (SpO2 %) were recorded at 0 min (prior to administration of any anaesthetic drug), immediately after induction of anaesthesia and thereafter at every 10 min intervals up to 50 min during maintenance period of anaesthesia by using vital signs monitor (multi-para monitor). The blood samples (2 mL) were collected from cephalic or recurrent tarsal vein (depending on site of IV cannula fixation) in sterile K_3EDTA vacutainer at 0 min (prior to administration of any anaesthetic drug), immediately after induction of anaesthesia and thereafter at every 15 min intervals up to 45 min during maintenance period of anaesthesia for haemato-biochemical studies. Haematological parameters, *viz.,* haemoglobin, packed cell volume, total erythrocyte count, total leucocyte count and differential leucocyte count were estimated using automatic haemato-analyser within 2 h after collection of blood samples. The blood glucose was estimated by using glucometer immediately after the blood collection. After haematological examination, remaining volume of blood sample was centrifuged at 700 x g for 10 min for separating plasma. The separated plasma was then collected and stored at -20° C in deep freezer for biochemical analysis, *viz.,* total protein, alanine aminotransferase, blood urea nitrogen and creatinine using semi-automatic biochemical analyser and standard kits.

Data obtained was analysed using R software version 4.0.3 to estimate the means. Means were compared using analysis of variance and Duncan's new multiple range test.

Results and Discussion

The study was conducted on 12 dogs (4 males and 8 females) of different breeds undergoing varied surgical interventions. The mean (±SE) age of the animals was 47.92±20.69 months ranging from 3 to 132 months and the mean (±SE) body weight was 21.38±4.77 kg ranging from 5.7 to 40 kg.

Successful endotracheal intubation was performed in all the animals of both groups immediately after induction of anaesthesia and the quality of induction anaesthesia was observed to be better with tiletamine-zolazepam combination (5 dog excellent, 1 good) than ketamine-diazepam combination (4 dog excellent, 1 good, 1 fair). Excellent score of induction was given for smooth and rapid transition from conscious to anaesthetized state with no resistance to opening of jaws and easy, quick intubation without loss of all reflexes responses; which was seen in five and four dogs of group I and II, respectively. There were two dogs (one each in group I and II) with good quality of induction score. One dog with fair quality of induction score in group II and required an additional dose (one third of induction dose) of ketamine-diazepam combination for intubation.

Quality of maintenance anaesthesia of isoflurane was found to be excellent with appropriate depth of anaesthesia, muscle relaxation and analgesia during surgery in both the groups with no statistical significant differences within and between the groups at different time intervals. Similarly, Kavechiya (2010) and Suthar (2016) reported excellent quality of maintenance anaesthesia using isoflurane with different induction anaesthetics.

Uneventful, smooth and rapid recovery was recorded in all the animals with mean (±SE) value of recovery time of 4.50±0.62 min in group I and 5.00±0.37 min in group II, with no significant difference between the groups. Duration of surgery, duration of maintenance anaesthesia and total duration of anaesthesia differed non-significantly between the groups.

There was no significant difference observed in the clinico-physiological parameters between the groups at different time intervals. Highly significant decrease in the mean value of rectal temperature was seen at different time intervals throughout the period of observation in both the groups (Table 1) from the baseline values. This might be due to the anaesthetic agents causing reduction in basal metabolic rate, depression of the thermoregulatory center, peripheral vasodilation, increased heat dissipation through respiratory system and inhibition of muscular activity (Diaz and Becker, 2010; Bindu *et al*., 2017). Similarly, drop in rectal temperature after administration of tiletamine-zolazepam was reported by Nam *et al.* (1993) and Pereira *et al.* (2019) and after ketamine-diazepam administration by Bornkamp *et al.* (2016).

Table 1: Mean (±SE) values of rectal temperature, pulse rate, respiratory rate and SpO_2 at different time intervals in dogs

Parameter	Time interval (min) after induction	Group I(n=6)	Group II(n=6)	p value
Rectal temperature (°F)	0 min (Base line)	101.22±0.18^{a}	101.72±0.14^{a}	0.06
	Immediately	100.10±0.34^{b}	100.10±0.34^{b}	1.00
	10 min	99.40±0.28^{bc}	99.35±0.21^{c}	0.89
	20 min	98.98±0.25^{c}	98.65±0.15^{d}	0.28
	30 min	98.20±0.20^{d}	97.95±0.15^{e}	0.35
	40 min	97.65±0.23^{d}	97.53±0.17^{e}	0.69
	50 min	96.62±0.33^{e}	96.82±0.14^{f}	0.58
	p value	0.0001	0.0001	
Pulse rate (beats/min)	0 min (Base line)	104.83±4.77^{f}	105.67±6.84^{f}	0.92
	Immediately	191.33±11.07^{a}	180.67±05.91^{a}	0.42
	10 min	177.83±6.38^{ab}	166.67±4.37^{ab}	0.18
	20 min	159.50±5.73^{bc}	155.67±5.61^{bc}	0.64
	30 min	146.67±4.66^{cd}	143.33±4.79^{cd}	0.63
	40 min	134.50±4.93^{de}	132.17±4.31^{de}	0.73
	50 min	122.83±5.79^{ef}	125.67±4.24^{e}	0.70
	p value	0.0001	0.0001	
Respiratory rate (breaths/min)	0 min (Base line)	39.83±2.93^{a}	38.00±2.83^{a}	0.66
	Immediately	27.67±1.20^{b}	24.50±4.35^{b}	0.50
	10 min	24.33±1.20^{bc}	24.33±2.65^{b}	1.00
	20 min	24.33±1.31^{bc}	22.00±2.68^{b}	0.45
	30 min	23.00±2.05^{bc}	22.00±1.37^{b}	0.69
	40 min	20.33±1.89^{c}	19.33±1.61^{b}	0.70
	50 min	22.00±1.63^{bc}	18.67±1.33^{b}	0.15
	p value	0.0001	0.0001	
Saturation percentage of oxygen (%)	0 min (Base line)	97.00±0.58^{a}	96.67±0.88^{a}	0.76
	Immediately	87.50±1.06$^{b}{}_{A}$	91.50±1.23$^{b}{}_{B}$	0.03
	10 min	95.83±1.19^{a}	94.67±0.76^{a}	0.43
	20 min	96.00±0.77^{a}	96.67±0.21^{a}	0.43
	30 min	96.67±0.42^{a}	96.33±0.80^{a}	0.72
	40 min	97.50±0.34^{a}	96.17±0.65^{a}	0.10
	50 min	97.17±0.48^{a}	95.83±0.79^{a}	0.18
	p value	0.0001	0.0006	

Means bearing different superscripts (a,b,c) within the group and different subscripts (A,B) between groups differ significantly ($p<0.05$) and highly significantly ($p\leq0.01$).

There was a highly significant increase in pulse rate and decrease in respiratory rate from baseline value after administration of induction anaesthetics, which got stabilized later during the maintenance anaesthetic period in both the groups non-significantly (Table 1). Similar findings were reported by Kavechiya (2010) and Hampton *et al.* (2019) after induction with ketamine-diazepam, tiletamine-zolazepam and with isoflurane maintenance. Highly significant decrease in mean values of saturation of peripheral oxygen (SpO_2) was noticed immediately after induction of anaesthesia from baseline values, which increased to the baseline levels during maintenance anaesthetic period (Table 1). Similarly, Chen *et al.* (2005) observed a drop in SpO_2 levels after administration of tiletamine-zolazepam; while, Kavechiya (2010) and Gangwar (2016) reported drop in SpO_2 values after administration of ketamine-diazepam in dogs. In the present study, endotracheal intubation was carried out in all the dogs immediately after induction of anaesthesia to maintain a patent airway followed by provision of 100 % oxygen along with the inhalation anaesthetic agent. This improved and maintained a stable oxygen level in the blood during maintenance period.

Highly significant differences in mean values of systolic, diastolic and mean arterial blood pressure were observed

within the groups (Table 2). The mean values of systolic, diastolic and mean arterial blood pressure increased immediately after induction of anaesthesia from baseline value and then gradually decreased over the maintenance period in both the groups. Similarly, Ramasamy (1995) observed an increase in blood pressure after administration of tiletamine-zolazepam; while, Ricco and Henao-Guerrero (2014) reported an increase in blood pressure after administration of ketamine in dogs.

There was no significant difference observed in the haematological parameters between the groups. Mean values of haemoglobin, packed cell volume and total erythrocyte count non-significantly decreased in both groups after administration of anaesthesia up to the end of the observations as compared to the baseline value (Table 3). This might be due to pooling of circulatory blood cells in the spleen or vasodilation produced by general anaesthesia leading to shifting of fluid from the extra-vascular compartment to the intravascular compartment to maintain normal cardiac output after administration of anaesthetic drugs (Sutil *et al*., 2017). Similarly, non-significant decrease in the mean values of haemoglobin, packed cell volume and total erythrocyte count were reported by Ramasamy (1995) and Chen *et al.* (2005) after administration of tiletamine-zolazepam combination and by Hampton *et al.* (2019) after administration of ketamine-diazepam anaesthesia in dogs, while Kavechiya (2010) and Hampton *et al.* (2019) reported gradual non-significant reduction in haemoglobin, packed cell volume and total erythrocyte concentration under isoflurane maintenance anaesthesia in dogs. Non-significant difference in the mean values of total leukocyte count (Table 3) and differential leucocyte count were observed at different time intervals in both the groups. The mean values of total leukocyte count and lymphocytes decreased from baseline value to 45 min after induction of anaesthesia; whereas, the mean values of neutrophils increased from baseline values up to 45 min after induction of anaesthesia in both the groups. Negligible differences in the mean values of monocytes and eosinophils were noticed at different time intervals in both the groups. This might be due to pooling of circulating blood cells in the spleen or subsequent effect

Table 2: Mean (±SE) values of systolic and diastolic blood pressure and mean arterial pressure at different time intervals in dogs

Parameter	Time interval (min) after induction	Group I (n=6)	Group II (n=6)	p value
Systolic blood pressure (mm Hg)	0 min (Base line)	147.50 ± 6.84^{bc}	146.33 ± 3.77^{c}	0.88
	Immediately	171.00 ± 10.23^{a}	186.33 ± 03.93^{a}	0.19
	10 min	$158.00\pm3.86^{ab}{}_{A}$	$173.33\pm4.05^{b}{}_{B}$	0.02
	20 min	$143.50\pm2.83^{bc}{}_{A}$	$158.00\pm4.49^{c}{}_{B}$	0.02
	30 min	$134.17\pm3.39^{cd}{}_{A}$	$146.83\pm3.38^{c}{}_{B}$	0.02
	40 min	119.83 ± 5.41^{de}	133.33 ± 3.28^{d}	0.06
	50 min	111.50 ± 6.58^{e}	122.33 ± 5.28^{d}	0.23
	p value	0.0001	0.0001	
Diastolic blood pressure (mm Hg)	0 min (Base line)	97.33 ± 4.83^{ab}	97.17 ± 6.55^{bc}	0.98
	Immediately	113.50 ± 4.62^{ab}	119.83 ± 4.12^{a}	0.33
	10 min	105.17 ± 5.51^{ab}	105.00 ± 2.35^{bc}	0.97
	20 min	84.33 ± 8.80^{bc}	91.17 ± 3.38^{c}	0.49
	30 min	69.33 ± 6.00^{cd}	75.83 ± 5.79^{d}	0.45
	40 min	63.00 ± 5.29^{de}	63.83 ± 4.50^{de}	0.90
	50 min	51.00 ± 5.63^{e}	58.17 ± 3.13^{e}	0.30
	p value	0.0001	0.0001	
Mean arterial pressure (mm Hg)	0 min (Base line)	114.00 ± 5.43^{bc}	113.50 ± 4.51^{c}	0.94
	Immediately	132.67 ± 5.47^{a}	142.00 ± 3.22^{a}	0.17
	10 min	122.67 ± 4.54^{ab}	127.83 ± 1.78^{b}	0.31
	20 min	104.00 ± 6.59^{cd}	113.50 ± 1.43^{c}	0.19
	30 min	91.00 ± 4.39^{de}	99.33 ± 3.57^{d}	0.17
	40 min	82.17 ± 4.24^{ef}	87.00 ± 2.78^{e}	0.36
	50 min	71.00 ± 5.71^{f}	79.50 ± 2.92^{e}	0.21
	p value	0.0001	0.0001	

Means bearing different superscripts (a,b,c) within the group and different subscripts (A,B) between groups differ significantly ($p<0.05$) and highly significantly ($p\leq0.01$).

Table 3: Mean (±SE) values of haematological parameters of balanced anaesthetic protocols at different time intervals in dogs

Parameter	Time interval (min) after induction	Group I (n=6)	Group II (n=6)	p value
Haemoglobin (g/dL)	0 min (Base line)	10.88±0.75	11.03±0.77	0.89
	Immediately	09.70±0.47	10.68±0.77	0.30
	15 min	08.80±0.72	10.40±0.75	0.16
	30 min	08.62±0.73	10.35±0.71	0.12
	45 min	08.25±0.73	10.27±0.75	0.08
	p value	0.08	0.95	
Packed cell volume (%)	0 min (Base line)	30.07±1.75	32.28±2.18	0.45
	Immediately	27.08±1.73	30.65±2.29	0.24
	15 min	26.03±1.83	30.15±2.03	0.16
	30 min	24.40±1.84	29.93±2.07	0.07
	45 min	22.80±1.73	26.48±3.96	0.41
	p value	0.07	0.63	
Total erythrocyte count (million/µL)	0 min (Base line)	5.24±0.38	5.26±0.53	0.98
	Immediately	4.65±0.28	5.00±0.45	0.53
	15 min	4.41±0.30	4.97±0.42	0.30
	30 min	4.21±0.36	4.89±0.36	0.22
	45 min	3.99±0.30	4.80±0.47	0.18
	p value	0.10	0.96	
Total leukocyte count (thousand/µL)	0 min (Base line)	18.23±2.91	19.15±1.56	0.79
	Immediately	15.38±2.19	18.57±1.46	0.25
	15 min	15.00±2.16	17.02±1.44	0.46
	30 min	14.47±2.40	16.05±1.55	0.59
	45 min	12.70±1.72	15.00±1.75	0.37
	p value	0.57	0.33	

None of the parameters differed significantly ($p>0.05$) between periods within the group or between groups.

of glucocorticoid on circulating blood cells (neutrophils and lymphocytes) attributed to anaesthetic effect on adrenocortical stimulation as reported by Brooks *et al*. (2022). However, these changes observed in haematological values were within the normal physiological range.

The biochemical parameters showed non-significant differences within the group and between the groups at different time intervals throughout the study period. Non-significant gradual increase in blood glucose was recorded from baseline value up to the end of anaesthetic observations in both the groups (Table 4). This might be due to surgical and anaesthetic stress that stimulates the hypothalamus and pituitary gland. This increases the secretion of adrenocortical hormone leading to production of glucocorticoids and a rise in blood glucose levels (Hernández-Avalos *et al*., 2021). The mean value of blood urea nitrogen was slightly increased during the entire anaesthetic study period from baseline values, within the normal physiological range. This might be due to temporary inhibitory effect of anaesthetic drugs on renal blood flow as reported by Riviere and Papich (2018). Total protein and alanine aminotransferase values were decreased non-significantly from baseline value up to the end in both the groups (Table 4). This might be due to the effect of anaesthesia which caused decrease cardiac output and proportional effect on decrease in total hepatic blood flow resulting in lower liver enzymes production as reported by Kumar *et al*. (2025). Minor alteration in the mean value of creatinine was recorded at different time intervals in both the groups. This might be due to the temporary inhibitory effect of anaesthetic drugs on renal blood flow and a consequent decrease in glomerular filtration rate (Lobetti and Lambrechts, 2020).

Few complications were observed after administration of anaesthetic drugs and during maintenance period in both the groups. Ptyalism was observed in one dog after administration of tiletamine-zolazepam which persisted even during the maintenance period in group I. There was mild resistance to opening of jaws and persistent pharyngeal and laryngeal reflexes during intubation in one animal each of group I and II. One dog in group II showed tongue curling, tight jaw tone and strong coughing reflex with intact swallowing and laryngeal reflexes accompanied by gagging reflex while intubation.

Table 4: Mean (±SE) values of blood biochemical constituents of balanced anaesthetic protocols at different time intervals in dogs

Parameter	Time interval (min) after induction	Group I (n=6)	Group II (n=6)	p value
Blood glucose (mg/dL)	0 min (Base line)	88.50±11.53	87.83±08.87	0.96
	Immediately	90.00±10.46	91.00±07.22	0.94
	15 min	91.50±9.68	95.50±7.97	0.76
	30 min	101.00±10.65	97.33±08.40	0.79
	45 min	111.33±13.00	104.67±08.60	0.68
	p value	0.57	0.66	
Total protein (g/dL)	0 min (Base line)	8.05±0.51	8.05±0.21	0.10
	Immediately	8.07±0.25	7.82±0.21	0.47
	15 min	7.37±0.53	7.60±0.19	0.69
	30 min	7.14±0.13	7.35±0.17	0.36
	45 min	6.94±0.11	7.54±0.29	0.08
	p value	0.11	0.22	
Alanine amino-transferase (IU/L)	0 min (Base line)	28.57±2.96	30.57±3.62	0.68
	Immediately	29.94±2.65	30.59±3.15	0.88
	15 min	28.77±1.85	30.90±3.56	0.61
	30 min	26.94±2.47	28.01±2.73	0.78
	45 min	26.48±1.21	24.76±1.57	0.41
	p value	0.82	0.56	
Blood urea nitrogen (mg/dL)	0 min (Base line)	12.87±1.53	11.83±2.02	0.69
	Immediately	13.88±1.67	12.95±2.14	0.74
	15 min	15.09±1.80	14.23±2.31	0.78
	30 min	16.88±2.33	15.51±2.75	0.71
	45 min	17.92±2.13	16.77±2.49	0.73
	p value	0.34	0.60	
Creatinine (mg/dL)	0 min (Base line)	1.15±0.09	1.05±0.07	0.37
	Immediately	1.13±0.03	1.05±0.06	0.21
	15 min	1.20±0.03	1.17±0.05	0.57
	30 min	1.26±0.04	1.20±0.05	0.35
	45 min	1.29±0.04	1.20±0.06	0.21
	p value	0.16	0.13	

None of the parameters differed significantly (p> 0.05) between periods within the group or between groups.

Conclusion

As per the findings of the present study, both tiletamine-zolazepam and ketamine-diazepam anaesthetic combinations produced fair to excellent quality of induction in dogs, However, tiletamine-zolazepam combination showed better quality of induction than ketamine-diazepam combination. Isoflurane provided excellent quality of maintenance anaesthesia with smooth and rapid recovery. Clinico-physiological parameters showed no significant difference between the groups but showed highly significant differences within the groups at variable intervals; while, haemato-biochemical parameters altered non-significantly within physiological limits after induction and during maintenance period from the baseline values between and within both the groups.

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