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Clinical adaptation of tiletamine-zolazepam for conducting different diagnostic and surgical procedures in dogs

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The objective of the study was to standardize the dose of tiletamine-zolazepam (Zoletil - 50®) in dogs followed by assessing the clinical adaptability of the standardized dose for various surgical manipulations. Twelve dogs were used in the study, among them 4 dogs were used to standardize the dose of tiletamine-zolazepam. The pilot doses of 3.3 mg/kg, 5 mg/kg, 6.6 mg/kg and 7 mg/kg body weight was administered intramuscularly up to satisfactory muscle relaxation with easy intubation. Out of which the dose of 7 mg/kg resulted in abolition of laryngeal reflex along with easy intubation. Thus, it was considered as standard dose and was further assessed for its adaptability in eight clinical cases. All the parameters were within the normal physiological range except for hypertension throughout the study period. In conclusion, tiletamine-zolazepam at the dose of 7 mg/kg body weight in dogs provided surgical restraint for 39.37±2.77 min without any adverse reactions with good recovery.

Key words: *Dissociative anaesthesia, Dog, Tiletamine-Zolazepam*

Dissociative anaesthesia is characterized by catalepsy and dissociation between the limbic system and thalamus i.e., by interrupting the ascending transmission of impulses from unconscious to conscious parts of the brain (Corssen *et al*., 1968; Lin *et al*., 1993). Tiletamine belongs to phencyclidine group of drugs, which does not provide muscle relaxation. Zolazepam, a benzodiazepine, has profound muscle relaxation with better amnesia, anticonvulsant and anxiolytic action. Combination of tiletamine and zolazepam is available commercially as a dry powder in 1:1 ratio popularly known as Zoletil-50®.

There are multiple studies showing the safety of ketamine-diazepam combination for sedation, analgesia and muscle relaxation in dogs. The drug combination of tiletamine-zolazepam is similar analogue to diazepam-ketamine combination. Tiletamine-zolazepam can be administered by intramuscular or intravenous route without any adverse side effects. The present study was done clinically to standardize the dose of tiletamine-zolazepam for induction and maintenance of adequate surgical restraint in dogs for performing various surgical interventions.

Materials and Methods

Client owned 12 dogs of mixed breed and of either sex presented for different diagnostic/surgical interventions were made the subjects of the study, and four among them were selected randomly for pilot study to standardize the dose of tiletamine-zolazepam alone without any premedication. The animals were categorized based on their health status in accordance with the American Society of Anesthesiologists (ASA) classification, surgery performed, age, gender and body weight (Table 1). Different physiological parameters were recorded before drug administration along with intravenous infusion of Ringer's lactate. All the pilot trial dogs were administered with tiletamine-zolazepam alone by intramuscular route at different doses of 3.3 mg/kg, 5 mg/kg, 6.6 mg/kg and 7.0 mg/kg body weight. All the dogs were monitored carefully for muscle relaxation, which was assessed by the degree of jaw relaxation, followed by an attempt to intubate. The time of successful intubation was taken as the time of induction. The dose of tiletamine-zolazepam which abolished laryngeal reflex was taken as standard dose, which was further administered in rest of the eight dogs. No anaesthetic agent was administered

Table 1: Patient classification.

Signalment	Group 1
Age (months)	42.37±16.99
Gender Male Female	71
Mean body weight (kg)	22.12±2.95
Surgical procedures	
Castration	2
Endoscopic procedures (otoscopy)	4
Radiographic positioning	1
Closed reduction of fracture	1
General condition	
ASA I	2
ASA II	6
Total	**8**

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and no top up dose of tiletamine-zolazepam was given throughout the surgical intervention. After the pilot trails, tiletamine-zolazepam @ 7.0 mg/kg body weight was selected for the induction in eight dogs presented for different surgical/diagnostic procedures.

Clinical parameters like rectal temperature (ºF), respiratory rate (breaths/min), heart rate (beats/min), position of eyeball, photo-pupillary reflex, oxygen saturation of haemoglobin (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), occurrence of nystagmus, palpebral reflex and occurrence of any respiratory abnormalities during the study were monitored before anaesthetic induction (t_0), just after intubation (t_1), 30 min post-intubation (t_{30}) and 60 min post-intubation (t_{60}). Other parameters like jaw relaxation and response to intubation was measured just after intubation. Anaesthetic responses such as response to intubation, jaw relaxation and pedal reflex were assessed based on the scoring system (Table 2). After observing the signs of recovery, various parameters such as extubation time, time of head raise, time of sternal recumbency and time of standing ataxia were recorded with quality of recovery on the basis of scoring system (Table 3).

GraphPad InStat® Software, Version 3.01, 32 bits was used for data analysis. Analysis of variance was done using student-Newman test for within group analysis from baseline value.

Results and Discussion

The dogs were classified according to surgery performed, body weight, gender and age as shown in Table 1. During the pilot study the dog showed abolition of laryngeal reflex and allowed to intubate when tiletamine-zolazepam was administered at 7 mg/kg body weight and it was used as the induction dose in 8 test dogs. Tiletamine-zolazepam provided excellent surgical restraint. More dose of tiletamine-zolazepam is required to induce anaesthesia when used alone. All the dogs became recumbent following administration of tiletamine-zolazepam and could be intubated without any difficulty (Chen *et al*., 2005).

The dogs showed excellent jaw relaxation and pedal reflex was intact though sluggish throughout the study. Mean±SE scores for jaw relaxation and pedal reflex was 2.87±0.12 and 1.00±0.00, respectively. Nam *et al*. (2013) reported that pedal reflex remain intact when tiletamine-zolazepam was used alone. In this study, the time to intubation was 7.87±0.87 min, the response to intubation was assigned score of 2.00±0.00 (Table 2). Position of eyeball was central in all the dogs at all time intervals. Corssen *et al.* (1968) reported that eyes became centrally positioned and had fixed gaze when dissociative anaesthetics were administered. Photo-pupillary reflex and palpebral reflex were intact throughout the study period from induction till recovery. Villamandos *et al*. (2013) documented that the dogs administered with low

Table 2: Scoring system for the subjective observations of various reflexes

Score reflex	0	1	2	3
Response to intubation	–	Difficult intubation, tube cannot be retained	Easy intubation with slight coughing or swallowing reflex following intubation but no gagging reflex	Intubation easily achieved with good muscle relaxation
Jaw relaxation	Not allowing to open jaws	Resistant to open and closes jaws quickly	Less resistant to open and closes jaws quickly	No resistance and jaws remained open
Pedal reflex	Intact and strong withdrawal of the limb	Intact but weak withdrawal of the limb	Intact but very weakwithdrawal of the limb	Complete abolishment of the reflex

Table 3: Scoring system for quality of recovery

Score	Quality	Character
4	Excellent	Assumes sternal recumbency with little or minimal struggling; stand and walk with minimal effort; no signs of anaesthetic effects.
3	Good	Some struggling; requires some assistance to stand; able to maintain balance once standing; minimal signs of residual anaesthetic effects.
2	Average	Some struggling; repeated attempts to stand and requires assistance to stand; very unstable while walking and unable to maintain balance; some signs of residual anaesthetic effects.
1	Poor	Prolonged struggling; unable to stand without assistance; hyperkinesia in response to manual assistance.

Table 4: Heart rate, respiration rate, rectal temperature, blood pressure and oxygen haemoglobin concentration in dogs administered with tiletamine-zolazepam at various time intervals.

Parameters	Time Interval			
	t_0	t_1	t_{30}	t_{60}
Heart rate (beats/min)	117.25±7.69	174.38±8.55***	154.63±7.68**	155.25±9.07**
Respiration rate (breaths/min)	28.62±4.45	21.37±1.33	19.87±1.80	23.50±2.38
Rectal temperature (ºF)	101.80±0.26	101.28±0.24	100.91±0.28	100.66±0.28*
Non-invasive blood pressure (mmHg)				
SBP	135.38±4.37	153.88±7.21	161.75±11.07	123.63±13.11
DBP	88.25±6.36	98.50±7.72	108.75±7.49	82.87±8.71
MAP	104.00±5.39	116.88±7.07	126.38±8.46	96.37±9.84
Oxygen haemoglobin concentration (SpO_2)	-	97.62±0.65	98.50±0.46	98.62±0.62

*The mean difference within the groups is significant when compared with base value (P<0.05); **The mean difference within the groups is significant when compared with base value (P<0.01); ***The mean difference within the groups is significant when compared with base value (P< 0.001).

doses of tiletamine-zolazepam and romifidine showed palpebral reflex. Nystagmus was not observed in any of the cases from intubation (t_1) up to end of the study period (t_{60}), but three dogs showed dorsoventral nystagmus during recovery.

Heart rate increased significantly from baseline value after induction (t_1) and then decreased significantly from (t_1) and remained below (t_1) up to end of the study (t_{60}) (Table 4). Significant increase in heart rate was reported in dogs receiving tiletamine-zolazepam alone, which was attributed to the sympathomimetic activity of tiletamine and blockade of nor-epinephrine reuptake causing rise in concentration of circulating catecholamine leading to stimulation of sinus node and elevation the heart rate (Koli *et al*., 2021).

Respiration rate reduced non-significantly from baseline (t_0-) value up to the end of the study (t_{60}). The lowest value was recorded 30 min after intubation (t_{30}). Tiletamine caused transient respiratory depression immediately after administration and given rise to an apneustic respiratory pattern characterized by deep breathing with irregular frequency and prolonged pauses (Pereira *et al*., 2019). Adverse respiratory abnormalities were not noticed in the present study.

Rectal temperature (ºF) decreased significantly from baseline value at t_{60}. Values of rectal temperature decreased every 10 min with a significant drop from 30 min. The drop in the temperature might be due to generalized sedation, reduction in metabolic rate and muscle relaxation (Ratnu *et al*., 2021; Koli *et al*., 2021).

Non-invasive blood pressure monitoring was done by recording SBP, DBP and MAP at different intervals from t_0 to t_{60}, which showed a non-significant increase from baseline up to 30 min (t_{30}) followed by non-significant decrease below baseline at 60 min (t_{60}). Hellyer *et al*. (1989) reported that tiletamine-zolazepam increased peripheral vascular resistance and thus caused significant increase in blood pressure when used at the dose of 6.6 mg/kg body weight.

Oxygen saturation of haemoglobin (SpO_2) increased non-significantly after intubation throughout the study period from t_1 to t_{60}. As all the animals were provided with fresh oxygen from intubation up to return of reflexes, the value of SpO_2 was maintained within the physiological limit.

Recovery was monitored by recording the time of extubation and time of head raise, time of return into sternal recumbency, time of standing ataxia without any assistance. Duration of all the recovery parameters were measured from successful intubation up to appearance of specific parameter. The mean±SE values of recovery parameters are shown in table 5. The overall quality of recovery was 2.75±0.16 based on the scoring system used (Table 3).

Table 5: Recovery parameters.

Parameters	Duration (in min)
Time of extubation	58.50±6.03
Time of head raise	63.87±6.71
Time of return into sternal recumbency	82.25±5.59
Time of standing ataxia	122.57±12.15

In conclusion, tiletamine-zolazepam @ 7.0 mg/kg body weight given by intramuscular route was suitable for smooth surgical restraint in dogs for mean±SE duration of 39.37±2.77 min. Tiletamine-zolazepam @ 7.0 mg/kg body weight did not show any adverse effects during recovery in all the animals.

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