RESEARCH ARTICLE

Evaluation of Tiletamine-Zolazepam Anaesthesia with Glycopyrrolate and Butorphanol as Preanaesthetics in Dogs

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Abstract

The study was conducted to evaluate the efficacy and feasibility of Tiletamine-Zolazepam anaesthesia (8 mg/kg b.wt., IV) with and without Glycopyrrolate, Butorphanol as preanesthetics in dogs undergoing ovario-hysterectomy. The study was conducted in 12 clinical cases of dogs in two groups, *viz.,* A and B with six dogs each. Group A animals were premedicated with Glycopyrrolate (10 µg/kg b.wt., IM) and Butorphanol (0.2 mg/kg b.wt., IM). In Group B no preanesthetics were administered. Onset of sedation was longer in Butorphanol (Group A) premedicated dogs, whereas the induction time, duration of anaesthesia, and recovery time were similar in both groups. Degree of analgesia was slightly longer in Group A. Degree of muscle relaxation and palpebral reflexes scores were almost similar in both the groups. Rectal temperature reduced slightly in both the groups till the end of anaesthetic period. Heart rate, respiratory rate increased significantly in both the groups, however, the values returned to baseline at the end of procedure. Electrocardiogram recorded sinus rhythm and tachycardia under the influence of Glycopyrrolate and Tiletamine. Hypertension was observed till 30th min and returned to baseline at the end of procedure. Haemato-biochemical parameters variations were non-significant in both the groups. Thus, it can be concluded that Tiletamine-Zolazepam can be safely administered to healthy patients undergoing elective surgical procedures, however, addition of Glycopyrrolate and Butorphanol could be helpful in preventing hypersalivation and provide certain extent of analgesia.

Key Words: Dog, Electrocardiogram, Glycopyrrolate, Hypertension, Tiletamine-Zolazepam.

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Introduction

Drug-induced unconsciousness known as general anaesthesia is characterized by regulated but reversible CNS depression, analgesia, and muscle relaxation, as well as attenuated sensory, motor, and autonomic responses (Thurmon and Short, 2014). The animals undergoing minor to major surgery are bound to receive general anaesthesia, including dogs and cats. There are inherent hazards to the lives of canine and feline patients under general anaesthesia, making it complex, and multifaceted treatment. The fatality rate in dogs and cats ranges from 0.1% to 1.35% under anaesthesia (Dyson *et al*., 1998). The choice of anaesthetic agents in veterinary practice is influenced by many factors including patient condition, familiarity with a specific anaesthetic regimen, cost, personnel record keeping, training of veterinarian and case load of practice (Kwon *et al*., 2003). When compared to inhalant anaesthetics, the injectable anaesthetics are more practical, affordable, safe for staff and environment friendly (Choi *et al*., 2012). There is a need to create an anaesthetic protocol that is safe not only for patient but also for doctors and the environment.

Balanced anaesthesia is induced by multiple drugs. Dissociative anaesthesia induces the dissociation between the thalamocortic and limbic systems and is characterized by a cataleptic state in which the eyes remain open and the swallowing reflexes remain intact (Thurmon and Short, 2014) and interfere with the transmission of incoming sensory information to the cerebral cortex, as well as communication between different sections of the central nervous system (CNS). Tiletamine-Zolazepam is a new injectable anaesthetic belongs to the class of dissociative anaesthetics and benzodiazepine sedative (Zolazepam) combination (1:1) that has several added advantages of Ketamine. Pre-anesthetic medications play an important role in anaesthetic management during induction, maintenance and recovery period. When used appropriately, these

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medications induce a desirable state of calm or sedation and reduced the pain. Butorphanol is a opioid analgesic and sedative believed to offer adequate visceral analgesia in the peri-operative period (Manocha *et al*., 2003). Glycopyrrolate is quaternary ammonium compound with anticholinergic effect used to prevent reflex bradycardia, reduce salivary secretion and facilitate a smooth intubation (Best, 2001). Glycopyrrolate, Butorphanol and Tiletamine-Zolazepam may be employed as balance anaesthetic technique in dogs undergoing elective surgery. Due to dearth of research on this injectable anaesthetic protocol in dogs, present clinical study was undertaken.

Materials and Methods

The study was carried out on 12 clinical cases of female dogs presented for ovario-hysterectomy at Department of Veterinary Surgery and Radiology, Veterinary College, Hassan (Karnataka, India). The dogs were divided into two equal groups A and B. Group A dogs were administered with preanesthetic drug inj. Glycopyrrolate @ 10 µg/kg b.wt., IM, followed 5 min later by inj. Butorphanol @ 0.2 mg/kg b.wt., IM. After 15 min, inj. Tiletamine-Zolazepam @ 8 mg/kg b.wt., IV was given. Group B dogs were administered with inj. Tiletamine-Zolazepam @ 8 mg/kg b.wt., IV without preanesthetic medication. Dogs of both the groups were intubated and ovariohysterectomy was performed as per standard surgical procedure.

Clinical parameters like sedation time (min), induction time (sec), duration of anaesthesia (min), and recovery time (min) were recorded. Also the degree of analgesia, degree of palpebral reflex and degree of muscle relaxation were recorded at 0^{th}, 5^{th}, 15^{th}, 30^{th}, 60^{th} and 90^{th} min interval of general anaesthesia.

In Group A dogs, sedation scoring from 0-3 was done as per Douet *et al.* (2018).Pedal reflex was recorded as a measure of depth of analgesia. As per Ahmad *et al.* (2011), the degree of analgesia was measured based on response given by the animal for pinching of inter-digital skin in the scale of 0-3. Degree of palpebral reflex was observed by blink in response to light tap on the medial or lateral canthus of eye in the scale of 0-3 as per Ahmad *et al.* (2011). Degree of muscle relaxation was observed by relaxation of abdominal muscles and reduced resistance to passive flexion of the limb in the scale of 0-3 as per Sachin (2018)

Physiological parameters like heart rate (beats/min), respiratory rate (breaths/min), rectal temperature (°F), electrocardiogram, blood pressure and haemato-biochemical parameters were recorded at 0^{th}, 5^{th}, 15^{th}, 30^{th}, 60^{th} and 90^{th} min interval of general anaesthesia.

The mean and standard errors for various parameters studied in both the groups were calculated using descriptive statistics. Recorded data was analysed by independent sample 't' test to compare between two groups. Anaesthetic scores between two groups were analyzed by non-parametric fisher exact test. General linear model repetitive ANOVA was undertaken to analyze data within group at various intervals.

Results and Discussion

Details of clinical, anaesthetic, physiological, and haemato-biochemical parameters are given in the Table 1, 2, 3 and 4, respectively.

Clinical Parameters

In group A dogs, there was a mild sedation as observed by Douet *et al.* (2018), however, group B dogs did not show any sedative effect. Induction time was non-significantly quicker in group A dogs compared to group B dogs. Duration of anaesthesia and recovery time was statistically non-significant between two groups (Table 1). After induction with Tiletamine-Zolazepam intravenously in dogs, reflexes like palpebral reflex, pharyngeal reflexes and laryngeal reflexes were present (Table 2), which concurred with the reports of Ryden *et al*. (2021) and Kucharski *et al.* (2022). Eye ball was centrally positioned with dilated pupils as a sign of dissociative anaesthetic state. Similar observations were reported by Rajankutty (1995). In both A and B groups, complete analgesia was recorded at 15^{th} and 30^{th} min and extended analgesic activity was observed in Group A dogs up to 90^{th} min and in group B dogs analgesic activity reduced from 60^{th} min onwards without significant differences between groups, except at 90^{th} min. According to Saha *et al.* (2007), Tiletamine produces analgesia by selective interruption of sensory inputs to the brain, while Wilson *et al.* (1992) opined that additive analgesic effect of Butorphanol and Tiletamine-Zolazepam might be due to the interaction at different spinal opiate sites. Present findings were similar to Lu *et al.* (2014), who reported that Tiletamine-Zolazepam provided complete analgesia at 30^{th} min and moderate analgesia at 5^{th}, 10^{th} and 80^{th} min in combination with opioid analgesic Tramdol and Xylazine. In both the groups, palpebral reflex was intact and weak not completely abolished because Tiletamine–zolazepam produces stable dissociative anaesthesia where it did not affect the cranial nerves and spinal reflexes (Kumar *et al*., 2006; Saha *et al*., 2007). Moderate degree of muscle relaxation was observed in both the groups with persistence of jaw tone throughout the study. Similar moderate myorelaxation was reported at 5^{th}, 15^{th}, 30^{th} min and mild myorelaxation at 60^{th} min by Pereira *et al.* (2019) in dogs. Persistent jaw tone in the present study concurred with Anjana *et al.* (2021). Kumar *et al.* (2006) reported that Tiletamine does not affect cranial nerve and spinal reflexes and its effect is devoid of muscle relaxation; the addition of Zolazepam achieves muscle relaxation.

Physiological Parameter

Physiological parameters of dogs in group A and B undergoing Tiletamine-Zolazepam anaesthesia are shown in Table 3. There was a pronounced tachycardia with normal

sinus rhythm. Reduction in PR and QT interval and alteration in the ST segment, T wave suggestive of myocardial hypoxia and it might be due to increase in heart rate, reduced diastolic period and coronary irrigation and decrease in oxygen supplied to myocardium. Similar observation was found by Rajankutty (1995), Tarraga *et al.* (2000). There was a significant increase in SAP, DAP and MAP in both the groups of dogs up to 30th min after administration of Tiletamine-Zolazepam and this might be due to direct CNS stimulation coupled with elevated sympathetic tone and also catecholamines are released from storage sites as a result of this process, rather than being reabsorbed into postganglionic nerve endings (Lee *et al.*, 2018). The time- and dose-dependent hypertension in Tiletamine-Zolazepam was consistent with the recognized cardio-stimulatory effects of dissociative anaesthetics (Wilson *et al.*, 1993). Rectal temperature decreased in both the groups and there was no statistical difference between the groups that was in line with Won *et al.* (2010) and Lu *et al.* (2014). Heart rate was increased significantly in both groups at 5th and 15th min after administration of Tiletamine-Zolaepam, but 30th min onwards heart rate was started to return to baseline value. Similar findings were mentioned by Hampton *et al.* (2019) and Koli *et al.* (2021). Increase in heart rate was due to sympathetic stimulation by the dissociative drugs (Krimins *et al.*, 2012). After induction with Tiletamine-Zolazepam in dogs, respiratory rate was decreased significantly at 5th min, in line with Pereira *et al.* (2019) and Koli *et al.* (2021), but 15th min onwards respiratory rate was increased throughout the study period, similar to observations of Hampton *et al.* (2019), and Landry and Maza (2020). After being administered intravenously, Tiletamine-Zolazepam caused hypoxemia and hypercarbia (Savvas *et al.*, 2005; Lee *et al.*, 2018). Like Ketamine, Tiletamine induces temporary or chronic tachypnoea (>40 breaths per min) throughout anaesthesia, a typical side effect of dissociative drugs in dogs (Savvas *et al.*, 2005; Landry and Maza 2020).

Table 1: Clinical parameters of dogs

Parameters	Group A	Group B
Onset of sedation (min)	11.83±0.91	---
Induction time (Sec)	9.67±1.12	10.5±1.09
Duration of anesthesia (min)	56.17±1.80	58.00±1.98
Recovery time (min)	124±1.13	126±1.53

Table 2: Anaesthetic parameters of dogs

Parameters	Group	Time interval					
		0th min	5th min	15th min	30th min	60th min	90th min
Degree of analgesia	Group A	00±00	2.67±0.21	3.00±0.0	3.00±0.00	2.33±0.21	1.00±0.00
	Group B	0.00±0.00	2.50±0.22	3.00±0.00	3.00±0.00	2.17±0.17	0.17±0.17
Degree of palpebral reflex	Group A	0.00±0.00	1.17±0.17	1.67±0.21	1.67±0.21	1.00±0.00	1.00±0.00
	Group B	0.00±0.00	1.00±0.00	1.50±0.22	1.50±0.22	1.00±0.00	1.00±0.00
Degree of muscle relaxation	Group A	0.00±0.00	2.50±0.22	2.83±0.17	2.17±0.17	1.00±0.00	0.00±0.00
	Group B	0.00±0.00	2.50±0.22	2.83±0.17	2.17±0.17	1.00±0.00	1.00±0.00

Table 3: Physiological parameters of dogs under Tiletamine-Zolazepam anaesthesia

Parameters	Group	Time interval					
		0th min	5th min	15th min	30th min	60th min	90th min
Heart rate (beats/ min)	Group A	116.33^{a}±0.94	134.17^{c}±0.99	142.17^{d}±0.91	122.83^{b}±0.86	121.50^{b}±0.99	117.00^{a}±0.82
	Group B	119.50^{a}±1.78	135.83^{c}±1.87	143.17^{d}±1.56	125.33^{b}±1.31	122.33^{ab}±1.28	118.83^{a}±1.47
Respiratory rate (b reaths/ min)	Group A	32.67±0.88	25.83±1.17	38.00±1.39	33.17±0.60	43.33±0.99	51.50±0.99
	Group B	34.17^{b}±1.87	27.33^{a}±1.15	36.33^{b}±0.95	35.00^{b}±1.15	45.83^{c}±1.87	52.33^{d}±1.89
Rectal temp. (°F)	Group A	102.1±0.08	101.61±0.13	100.91±0.21	100.52±0.04	99.88±0.20	99.68±0.12
	Group B	102.38^{c}±0.25'	101.23^{c}±0.28	101.23^{b}±0.19	100.98^{b}±0.18	100.21^{a}±0.23	99.82^{a}±0.27
Systolic pressure (mmHg)	Group A	139.33±1.71	157.50±1.89	165.00±1.98	155.33±1.71	143.67±0.67	139.83±1.51
	Group B	135.33^{a}±1.36	153.17^{c}±1.83	162.00^{d}±1.00	151.67^{c}±1.20	142.00^{b}±0.86	135.67^{a}±1.58
Diastolic pressure (mmHg)	Group A	99.83±1.17	109.83±0.95	104.00±1.18	101.00±1.44	100.67±0.88	100.33±0.84
	Group B	97.17^{a}±1.08	112.17^{d}±0.95	106.67^{c}±1.02	101.67^{b}±0.67	100.67^{b}±0.42	101.00^{b}±0.45
Mean heart pressure (mmHg)	Group A	118.50±0.85	133.17±1.42	127.50±1.71	124.17±2.10	116.83±1.62	107.00±1.41
	Group B	117.17±0.60	138.67±2.85	130.17±1.17	125.00±1.41	116.33±0.61	106.33±1.20

Means bearing different superscripts within group at different intervals vary significantly (p≤0.05).

Table 4: Haemato-biochemical parameters of dogs under Tiletamine-Zolazepam anaesthesia

Parameters	Group	Time interval					
		0th min	5th min	15th min	30th min	60th min	90th min
Hb (g/dL)	Group A	13.33±0.47	13.40±0.21	12.63±0.09	12.40±0.14	12.10±0.19	12.07±0.21
	Group B	12.80±0.34	12.60±0.29	12.60±0.6	12.40±0.03	12.20±0.09	12.50±0.06
PCV (%)	Group A	36.88±0.25	36.63±0.86	35.23±0.36	34.88±0.67	34.73±0.32	34.85±0.18
	Group B	36.95±0.14	36.48±0.23	35.78±0.23	34.93±0.39	34.92±0.27	34.88±0.20
TEC ($\times10^6$/µL)	Group A	6.20±0.29	5.39±0.20	5.56±0.30	5.22±0.18	5.55±0.35	5.30±0.21
	Group B	6.49±0.26	5.55±0.30	5.58±0.23	5.52±0.16	5.33±0.14	5.44±0.14
TLC ($\times10^3$/µL)	Group A	11.87±0.38	11.72±0.17	11.30±0.13	10.75±0.29	10.42±0.19	10.28±0.09
	Group B	11.68±0.12	11.83±0.11	11.43±0.07	11.07±0.29	10.18±0.20	10.18±0.06
Platelet count ($\times10^3$/µL)	Group A	3.82±0.21	3.60±0.32	3.25±0.41	3.22±0.41	3.11±0.41	2.94±0.37
	Group B	3.48±0.10	3.49±0.06	3.27±0.26	3.20±0.16	3.14±0.27	2.93±0.25
Neutrophils (%)	Group A	83.17±0.83	83.17±0.91	84.33±0.61	85.00±0.37	85.17±0.79	86.50±0.62
	Group B	83.33±0.49	83.67±0.84	84.17±0.75	85.17±087	85.33±0.95	86.17±0.65
Lymphocytes (%)	Group A	14.50±0.20	14.00±0.31	14.00±0.31	14.00±0.00	12.00±0.33	11.00±0.68
	Group B	14.83±0.40	14.67±0.61	14.67±1.20	14.17±1.22	12.67±1.05	11.00±1.21
Eosinophils (%)	Group A	1.00±0.00	1.00±0.00	0.00±0.00	0.00±0.00	1.00±0.00	1.00±0.00
	Group B	1.00±0.00	1.00±0.00	0.00±0.00	0.00±0.00	1.00±0.00	1.00±0.00
Monocytes (%)	Group A	2.00±0.00	2.00±0.00	1.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00
	Group B	2.00±0.00	2.00±0.00	1.00±0.00	2.00±0.00	2.00±0.00	2.00±0.00
ALT (IU/L)	Group A	27.05±0.35	27.58±0.95	27.50±1.31	26.22±1.34	26.38±1.43	26.63±1.56
	Group B	26.58±2.02	26.35±0.21	26.12±1.46	26.28±0.83	26.03±0.51	26.45±0.57
AST (IU/L)	Group A	45.60±0.74	45.97±0.50	45.13±0.64	45.58±1.22	45.43±1.17	45.40±1.61
	Group B	46.77±0.64	45.22±1.03	45.88±1.33	44.47±0.98	44.15±2.20	45.52±1.21
BUN (mg/dL)	Group A	13.10±0.22	12.78±0.14	12.52±0.09	12.30±0.08	12.05±0.10	11.75±0.12
	Group B	13.23±0.19	12.85±0.15	12.48±0.09	12.28±0.09	12.12±0.07	11.83±0.06
Creatinine (mg/dL)	Group A	1.00±0.01	0.98±0.01	1.01±0.01	1.01±0.01	1.00±0.01	1.02±0.01
	Group B	0.99±0.01	0.99±0.01	1.02±0.00	1.01±0.01	1.01±0.01	1.03±0.00
Total protein (g/dL)	Group A	6.73±0.22	6.64±0.23	6.75±0.24	6.64±0.24	6.62±0.21	6.62±0.21
	Group B	7.19±0.18	7.08±0.18	7.15±0.12	6.91±0.15	6.80±0.16	6.97±0.12
Blood glucose (mg/dL)	Group A	97.00±0.98	107.33±0.75	108.67±0.97	98.17±0.88	97.83±0.96	100.83±0.96
	Group B	99.17±1.42	107.67±1.94	106.83±0.75	101.83±1.76	100.33±1.20	101.00±0.97

Haemato-Biochemical Parameters

In both the groups there was a non-significant decrease in haemoglobin, PCV, TEC, TLC and lymphocyte and non-significant elevation in neutrophil count (Table 4). These findings are in accordance with Ranpariya *et al*. (2013), Arya *et al*. (2021), and Koli *et al.* (2021). There was a non-significant variation in alanine aminotransferase, aspartate aminotransferase, serum creatinine, blood urea nitrogen, total protein and blood glucose level (Table 4) and those variations were within the normal physiological limit.

Conclusions

Tiletamine-Zolazepam with Glycopyrrolate and Butorphanol preanaesthetics had beneficial effect in counteracting hypersalivation and provided a certain extent of post-operative analgesia as compared to Tiletamine-Zolazepam alone in dogs.

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